UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

WYETH, Plaintiff, v. IMPAX LABORATORIES, INC.. Defendant.	Civil Action No. 06-222 (JJF) **PUBLIC VERSION**

DECLARATION OF MARY B. MATTERER IN SUPPORT OF IMPAX LABORATORIES, INC.'S MOTIONS FOR SUMMARY JUDGMENT

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Original Date: November 30, 2007
Public Version: December 7, 2007

I, MARY MATTERER, declare and state that:

1. I am a partner at the law firm of Morris James LLP, counsel to Defendant Impax Laboratories, Inc.

2. Attached hereto as Exhibit 1 is a true and correct copy of U.S. Patent 4,535,186 issued August 13, 1985.

3. Attached hereto as Exhibit 2 is a true and correct copy of an excerpt of NDA 20-699 re "Item 2. Application Summary – Integrated Summary of Benefits and Risks" (WYETH004-00299-304).

4. Attached hereto as Exhibit 3 is a true and correct copy of a Project Authorization Request prepared by Deborah Sherman (WYETH012-000034-037).

5. Attached hereto as Exhibit 4 is a true and correct copy of the relevant excerpts of the September 11, 2007 deposition of Eliseo Salinas, Ph.D.

6. Attached hereto as Exhibit 5 is a true and correct copy of the relevant excerpts of the May 18 and November 15, 2007 depositions of Robin Enever, Ph.D.

7. Attached hereto as Exhibit 6 is a true and correct copy of Wyeth-Ayerst Research General Technical Report No. 27216 (WYETH004-000326-361).

8. Attached hereto as Exhibit 7 is a true and correct copy of the relevant excerpts of the January 14, 2005 deposition of Douglas Smith in re *Wyeth v. Teva Pharmaceuticals, USA Inc.*

9. Attached hereto as Exhibit 8 is a true and correct copy of an April 29, 1991 Memorandum authored by Douglas Smith (WYETH010-003652-655).

10. Attached hereto as Exhibit 9 is a true and correct copy of the relevant excerpts of the August 3, 2007 deposition of Deborah M. Sherman.

11. Attached hereto as Exhibit 10 is a true and correct copy of the relevant excerpts of the Laboratory Notebook of Deborah Sherman (WYETH009-000008-009, 061, 064, 073, 105, and 120).

12. Attached hereto as Exhibit 11 is a true and correct copy of U.S. Patent 6,274,171 B1, issued August 14, 2001.

13. Attached hereto as Exhibit 12 is a true and correct copy of a June 5, 1993 Memorandum authored by Dr. Richard DeNeale (WYETH053-001462-463).

14. Attached hereto as Exhibit 13 is a true and correct copy of a January 9, 1992 Memorandum authored by Dr. Richard DeNeale (WYETH053-001323-325).

15. Attached hereto as Exhibit 14 is a true and correct copy of an October 20, 1992 Memorandum authored by Bill House (WYETH 203-028374-380).

16. Attached hereto as Exhibit 15 is a true and correct copy of the relevant excerpts of the Laboratory Notebook of John Clark (WYETH007-000259, 260, 263, 271, 274, and 278).

17. Attached hereto as Exhibit 16 is a true and correct copy of U.S. Patent 4,138,475 issued February 6, 1979.

18. Attached hereto as Exhibit 17 is a true and correct copy of the relevant excerpts of the November 8, 2007 deposition of Richard DeNeale, Ph.D.

19. Attached hereto as Exhibit 18 is a true and correct copy of a document entitled "Venlafaxine ER Hydrogel Tablet Work" (WYETH155-000140-144).

20. Attached hereto as Exhibit 19 is a true and correct copy of Dr. Salinas's Responses to Topics for Deposition of Wyeth, September 11. 2007 (Salinas Deposition Exhibit 335).

21. Attached hereto as Exhibit 20 is a true and correct copy of a Wyeth-Ayerst Research General Medical Report No. 23446 re Protocol No. 600B-127-US (WYETH004-001803).

22. Attached hereto as Exhibit 21 is a true and correct copy of a Wyeth-Ayerst Research General Medical Report No. 24775 re Protocol No. 600B-134-US (WYETH022-001711-714, 001736, 001741-743, 001761-763).

23. Attached hereto as Exhibit 22 is a true and correct copy of International Patent Application WO 94/27589 (Edgren Deposition Exhibit 345).

24. Attached hereto as Exhibit 23 is a true and correct copy of the relevant excerpts of the October 11, 2007 deposition of David Edgren.

25. Attached hereto as Exhibit 24 is a true and correct copy of U.S. Patent No. 6,440,457 issued August 27, 2002.

26. Attached hereto as Exhibit 25 is a true and correct copy of the Complaint in re *Alza Corp. v. Wyeth*, Case No. 9:06-CV-00156 (E.D. TX.).

27. Attached hereto as Exhibit 26 is a true and correct copy of a Request for *Ex Parte* Reexamination re U.S. Patent No. 6,440,457 (Reeaxamination Control No.90/008142), dated July 28, 2006.

28. Attached hereto as Exhibit 27 is a true and correct copy of a February 16, 2007 Ex Parte Reexamination Communication Transmittal Form re Reeaxamination Control No. 90/008142.

29. Attached hereto as Exhibit 28 is a true and correct copy of the PTO Docket Sheet related to Reexamination Control No. 90/008,142.

30. Attached hereto as Exhibit 29 is a true and correct copy of a Wyeth-Ayerst Research General Medical Report No. 26165 re Protocol No. 600B-208-US (WYETH004-013233-238, 013318-19).

31. Attached hereto as Exhibit 30 is a true and correct copy of a Wyeth-Ayerst Research General Medical Report No. 27758 re Protocol No. 600B-209-US (WYETH004-014377-381).

32. Attached hereto as Exhibit 31 is a true and correct copy of a Wyeth-Ayerst Research General Medical Report No. 25782 re Protocol No. 600B-367-US (WYETH004-015397-523).

33. Attached hereto as Exhibit 32 is a true and correct copy of the relevant excerpts of the November 28, 2007 deposition of Ronald Thisted (rough transcript).

34. Attached hereto as Exhibit 33 is a true and correct copy of U.S. Patent 6,403,120 B1 issued June 11, 2002.

35. Attached hereto as Exhibit 34 is a true and correct copy of U.S. Patent 6,419,958 B2 issued July 16, 2002.

36. Attached hereto as Exhibit 35 is a true and correct copy of the Certified File History re Patent Application 08/821,137 (WYETH022-000790, 000804-805, 000850-851, 000907, 000911).

37. Attached hereto as Exhibit 36 is a true and correct copy of the Certified File History re Patent Application 08/964,328 (WYETH002-000563, 000580-583, 000715-720).

38. Attached hereto as Exhibit 37 is a true and correct copy of U.S. Patent No. 5,506,270 issued April 9, 1996.

39. Attached hereto as Exhibit 38 is a true and correct copy of an excerpt of Impax's ANDA re "Section VI Bioavailability/Bioequivalence" (IMPAX003789 – 3791).

40. Attached hereto as Exhibit 39 is a true and correct copy of an excerpt from the Expert Report of Ronald J. Sawchuk, Ph.D. dated September 28, 2007.

41. Attached hereto as Exhibit 40 is a true and correct copy of an April 13, 2007 Letter to Linda A. Wadler from Samuel F. Ernst re Impax's Proposed Claim Constructions.

42. Attached hereto as Exhibit 41 is a true and correct copy of the PTO's Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR Int'l Co. v. Teleflex Inc.*, Fed. Reg. Vol. 72, No. 195, dated October 10.2007.

43. Attached hereto as Exhibit 42 is a true and correct copy of the Rebuttal Report of Dr. Henry G. Grabowski, dated October 31, 2007.

44. Attached hereto as Exhibit 43 is a true and correct copy of a July 26, 1993 Memorandum authored by Albert T. Derivan, M.D. (WYETH020-006616-618).

45. Attached hereto as Exhibit 44 is a true and correct copy of the relevant excerpts of the October 20, 2004 Deposition of Deborah Sherman in re *Wyeth v. Teva Pharmaceuticals USA, Inc.*

46. Attached hereto as Exhibit 45 is Wyeth's Response to Interrogatory No. 28, served October 10, 2006.

47. Attached hereto as Exhibit 46 is a true and correct copy of the relevant excerpts of the October 14, 2004 Deposition of John Lamer in re *Wyeth v. Teva Pharmaceuticals USA, Inc.*

48. Attached hereto as Exhibit 47 is a true and correct copy of the Rebuttal Expert Report of Arthur H. Kibbe, dated October 31, 2007.

49. I declare under penalty of perjury under the laws of the state of Delaware that the foregoing is true and correct to the best of my knowledge and that this declaration was executed on this 30th day of November, 2007 at Wilmington, Delaware.

By: 
MARY B. MATTERER (I.D. No. 2696)

Exhibit 1

United States Patent [19]

Husbands et al.

[11] **Patent Number: 4,535,186**

[45] **Date of Patent: Aug. 13, 1985**

[54] **2-PHENYL-2-(1-HYDROXYCYCLOALKYL OR 1-HYDROXYCYCLOALK-2-ENYL)ETHYLAMINE DERIVATIVES**

[75] Inventors: **G. E. Morris Husbands, Berwyn; John P. Yardley, Gulph Mills; Eric A. Muth, West Chester, all of Pa.**

[73] Assignee: **American Home Products Corporation, New York, N.Y.**

[21] Appl. No.: **545,701**

[22] Filed: **Oct. 26, 1983**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 486,594, Apr. 19, 1983, abandoned, which is a continuation-in-part of Ser. No. 449,032, Dec. 13, 1982, abandoned.

[51] **Int. Cl.**[3] **C07C 87/28**

[52] **U.S. Cl.** ..... **564/336**; 560/140; 560/250; 560/251; 560/252; 564/157; 564/219; 564/220; 549/443; 549/444; 549/440; 260/465 E

[58] **Field of Search** ..... 564/336, 157, 219, 220; 260/465 E; 560/250, 251, 252, 140; 549/443, 444

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,132,179	5/1964	Clarke	564/355
3,758,527	9/1973	Marxer	560/250
3,847,950	11/1974	Suh et al.	260/340.5 R
3,928,626	12/1975	Yardley et al.	424/330
3,974,157	8/1976	Shetty et al.	260/247.2 B
3,979,444	9/1976	Lednicer	560/250
4,269,788	5/1981	Muller	564/305

FOREIGN PATENT DOCUMENTS

0737473	6/1966	Canada	564/305
1124485	3/1962	Fed. Rep. of Germany .	
6408M	10/1968	France .	

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Maillard et al., Bull. Soc. Chim. France (1976), No. 6, pp. 2110–2116.

Kvam, Clinical Therapeutics, 2 Suppl. B (1979), pp. 1–12.

Mutak et al., Acta Pharm. Jugosl., 31, 17–26 (1981).

Mutak et al., ibid, 31, 143–150 (1981).

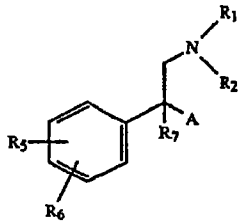
Rajsner et al., Coll. Czech. Chem. Comm., 28, 1031–1043 (1963).

Primary Examiner—Nicky Chan

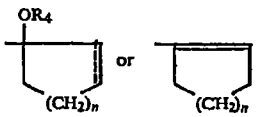
Attorney, Agent, or Firm—Richard K. Jackson

[57] **ABSTRACT**

This invention provides a group of hydroxycycloalkanephenethyl amine antidepressant derivatives of the following structural formula:



in which A is a moiety of the formula



where

the dotted line represents optional unsaturation;

R_1 is hydrogen or alkyl;

R_2 is alkyl;

R_4 is hydrogen, alkyl, formyl or alkanoyl;

R_5 and R_6 are, independently, hydrogen, hydroxyl, alkyl, alkoxy, alkanoyloxy, cyano, nitro, alkylmercapto, amino, alkylamino, dialkylamino, alkanamido, halo, trifluoromethyl or, taken together, methylenedioxy;

R_7 is hydrogen or alkyl; and

n is 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt thereof.

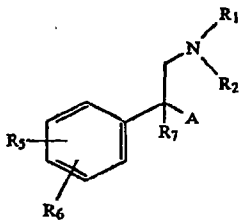
32 Claims, No Drawings

2-PHENYL-2-(1-HYDROXYCYCLOALKYL OR 1-HYDROXYCYCLOALK-2-ENYL)ETHYLAMINE DERIVATIVES

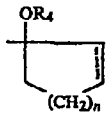
This application is a continuation-in-part of U.S. patent application Ser. No. 486,594, filed Apr. 19, 1983, now abandoned, which application is a continuation-in-part of U.S. patent application Ser. No. 449,032, filed Dec. 13, 1982, now abandoned.

DESCRIPTION OF THE INVENTION

In accordance with this invention there is provided a group of substituted phenethylamine derivatives which are central nervous system antidepressants. The compounds of this invention present the following structural formula:



in which A is a moiety of the formula



where

the dotted line represents optional unsaturation, or the analogous cycloalkenyl moiety

R_1 is hydrogen or alkyl of 1 to 6 carbon atoms;

R_2 is alkyl of 1 to 6 carbon atoms;

R_4 is hydrogen, alkyl of 1 to 6 carbon atoms, formyl, or alkanoyl of 2 to 7 carbon atoms;

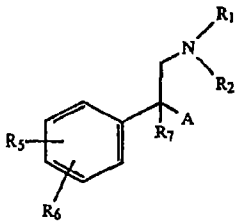
R_5 and R_6 are independently hydrogen, hydroxyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, cyano, nitro, alkylmercapto of 1 to 6 carbon atoms, amino, alkylamino of 1 to 6 carbon atoms, dialkylamino in which each alkyl group is of 1 to 6 carbon atoms, alkanamido of 2 to 7 carbon atoms, halo, trifluoromethyl, or, when taken together, methylene dioxy;

R_7 is hydrogen or alkyl of 1 to 6 carbon atoms; and

n is one of the integers 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt thereof.

The preferred compounds are those of the formula:



in which

A is defined supra;

R_1 is hydrogen or alkyl of 1 to 3 carbon atoms;

R_2 is alkyl of 1 to 3 carbon atoms;

R_5 is hydrogen, hydroxy, alkoxy of 1 to 3 carbon atoms, chloro, bromo, trifluoromethyl or alkyl of 1 to 3 carbon atoms;

R_6 is alkyl of 1 to 3 carbon atoms, alkoxy of 1 to 3 carbon atoms, chloro, bromo, trifluoromethyl or alkanoyloxy of 2 to 3 carbon atoms.

R_7 is hydrogen or alkyl of 1 to 3 carbon atoms;

or a pharmaceutically acceptable salt thereof.

The most preferred compounds are those in which R_5 and R_6 are in meta or para positions and n is 2.

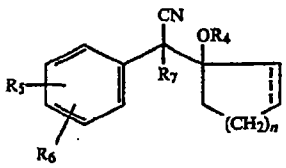
The compounds in which R_4 is formyl or alkanoyl of 2 to 7 carbon atoms are not nearly as potent as the corresponding free hydroxy bearing derivatives in the test procedures employed and disclosed herein. However, in long term therapy the acyloxy derivatives will act as pro drugs as the acyl group is removed in vivo either via acid hydrolysis in the stomach or enzymatically.

The pharmaceutically acceptable acid addition salts of the basic compounds of this invention are formed conventionally by reaction of the free base with an equivalent amount of any acid which forms a non-toxic salt. Illustrative acids are either inorganic or organic, including hydrochloric, hydrobromic, fumaric, maleic, succinic, sulfuric, phosphoric, tartaric, acetic, citric, oxalic and similar acids. For parenteral administration, the use of water soluble salts is preferred, although either the free base of the pharmaceutically acceptable salts are applicable for oral or parenteral administration of the antidepressant agents of this invention. The halo substituent representing R_5 or R_6 is intended to include the chloro, bromo, iodo or fluoro substituents.

The compounds of this invention are produced by reaction of a cycloalkanone or a cycloalkenone with an appropriately substituted (ortho or para) phenylacetonitrile anion following the procedure of Sauvetre et al., Tetrahedron, 34, 2135 (1978) followed by reduction (catalytic hydrogenation, borane reducing agents, $LiAlH_4$, etc.) of the nitrile to a primary amine and alkylation of the amine. In the presence of cyclo aliphatic unsaturation, lithium aluminum hydride is the preferred reducing agent. Subsequent acylation of the α-cycloaliphatic-hydroxyl group and any phenolic hydroxyl group present may be effected conventionally with a formylating agent such as formyl fluoride or an alkanoic acid halide or anhydride. Symmetrical N-methylation may be accomplished via a modified Eschweiler-Clarks procedure employing a large excess of water as illustrated by Tilford et al., J.A.C.S. 76, 2431 (1954); alternatively the procedure of Borch and Hassid, J. Org. Chem., 37, 1653 (1972) using sodium cyanoborohydride and formaldehyde may be employed. Non-symmetrical

N-alkylation or monoalkylation may be accomplished by stepwise alkylation of the N-trifluoroacetate as illustrated by R. A. W. Johnstone et al., J. Chem. Soc., (C) 2223 (1969). Where R_4 is alkyl it is introduced prior to reduction of the nitrile by conventional O-alkylation.

The intermediate nitriles prepared during the production of the antidepressant agents of this invention represent an additional aspect of the invention. They are depicted by the structural formula:



in which

the dotted line represents optional unsaturation, and

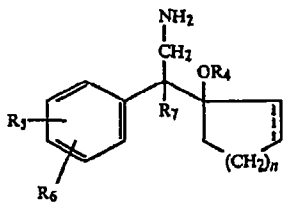
R_4 is hydrogen or alkyl of 1 to 6 carbon atoms;

R_5 and R_6 are ortho or para substituents, independently selected from the group consisting of hydrogen, hydroxyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, aralkoxy of 7 to 9 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, alkylmercapto of 1 to 6 carbon atoms, halo or trifluoromethyl;

R_7 is hydrogen or alkyl of 1 to 6 carbon atoms; and

n is one of the integers 0, 1, 2, 3 or 4.

The intermediate primary amines produced by reduction of the nitrile depicted in the preceding paragraph represent an additional aspect of the invention. They present the following structural formula:



in which

the dotted line represents optional unsaturation,

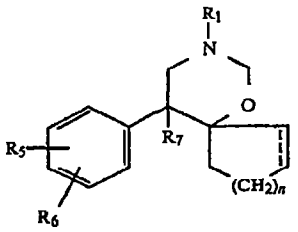
R_4 is hydrogen, or alkyl of 1 to 6 carbon atoms;

R_5 and R_6 are ortho or para substituents independently selected from the group consisting of hydrogen, hydroxyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, aralkoxy of 7 to 9 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, alkylmercapto of 1 to 6 carbon atoms, halo or trifluoromethyl;

R_7 is hydrogen or alkyl of 1 to 6 carbon atoms; and

n is one of the integers 0, 1, 2, 3 or 4.

Symmetrical N,N-dimethylation may be performed readily by reaction of the primary amino derivative with formaldehyde, formic acid in a large excess of water. An intermediate, 3-aza-1-oxaspiro[5.5]undecane, which represents an additional intermediate of this invention is formed during the reaction and is isolatable. It presents the following structural formula:



in which the dotted line represents optional unsaturation,

R_1 is methyl;

R_5 and R_6 are orthor or para substituents independently selected from the group consisting of hydrogen, hydroxyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, aralkoxy of 7 to 9 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, alkylmercapto of 1 to 6 carbon atoms, halo or trifluoromethyl;

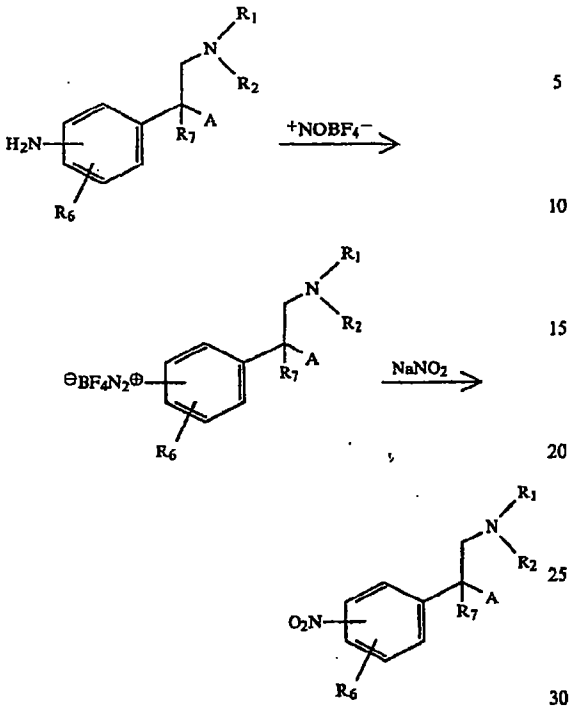
R_7 is hydrogen or alkyl of 1 to 6 carbon atoms; and

n is one of the integers 0, 1, 2, 3 or 4.

These oxaspiro[5.5]undecane intermediates possess similar activity to the corresponding open-ring tertiary amino end compounds of the invention. For example, the oxazine produced in Example 3 is hereinafter compared, in its properties, with the corresponding dimethylamino end compound of Example 3. The end compound is produced from the corresponding oxazine by prolonged reflux in the presence of aqueous formic acid.

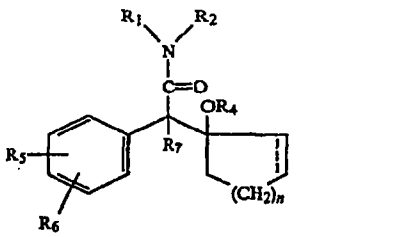
An alternative, and preferred, mode of preparing the compounds of this invention involves the reaction of a cycloalkanone or cycloalkenone with an appropriately substituted phenylacetamide anion following the procedure of Sauvetre et al., ibid., followed by reduction of the amide with lithium aluminum hydride or a borane reducing agent, except in the case of cycloaliphatic unsaturation as discussed, supra, to the corresponding amine. This process is preferred because it is considerably more facile when dealing with meta-substituted or halo-substituted phenylacetamide reactants which pose some problems when proceeding through the acetonitrile intermediate. This route to the desired end products also permits one to readily vary the valued R_1 and R_2 in the initial reactant.

The cyano substituent representing R_5 and/or R_6 is introduced after all reduction steps have been completed by displacement of an R_5-R_6 halo substitution with cuprous cyanide. The amino substituents representing R_5 and/or R_6 are protected throughout the reaction sequence with a protecting group such as 1,1,4,4-tetramethyl-1,4-dichlorosilylethylene which completely blocks the amino nitrogen atom from undesireable reactions. After completion of the reaction sequence, the amino group is deprotected and alkylated or acylated by conventional means to provide a mono- or di-alkylamine or an alkanamido group in each case of 1 to 6 carbon atoms. The nitro substituent representing R_5 and/or R_6 is introduced as an aromatic substituent by diazotization of the aromatic amine followed by treatment with alkali metal nitrite in the presence of copper or by formation of the diazonium tetrafluoroborate and reaction with an alkali metal nitrite, thusly:



The cyano substituent may be introduced via the diazonium salt with cyprous cyanide in analogous manner.

The intermediate amide represents an additional aspect of this invention and is depicted by the following structural formula:



in which

the dotted line represents optional unsaturation,

R_1 is hydrogen or alkyl of 1 to 6 carbon atoms;

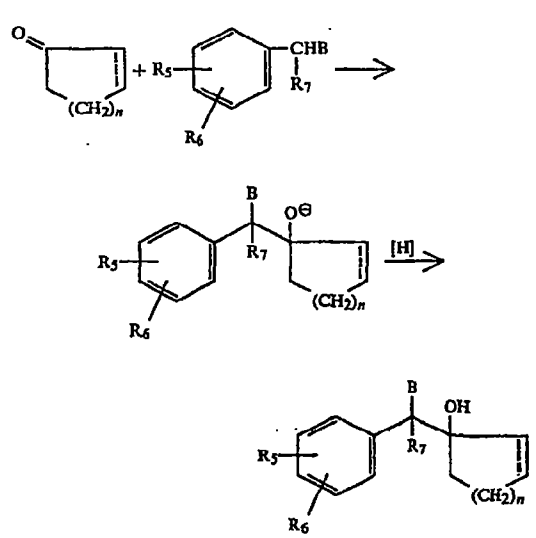
R_2 is alkyl of 1 to 6 carbon atoms;

R_4 is hydrogen or alkyl of 1 to 6 carbon atoms;

R_5 and R_6 are, independently, hydrogen, hydroxyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, aralkoxy of 7 to 9 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, alkylmercapto of 1 to 6 carbon atoms, N-protected amino, halo, trifluoromethyl, or when taken together, methylenedioxy;

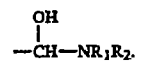
R_7 is hydrogen or alkyl of 1 to 6 carbon atoms; and n is one of the integers 0, 1, 2, 3 or 4. When R_4 is alkyl it is introduced prior to reduction. The protecting group employed to prevent reaction at the amino substituent representing R_5 and/or R_6 is any protecting group that will completely prevent reaction at a primary $—NH_2$ substituent, such as 1,2-[bis-dimethyl-silylchloride]ethane.

More indirect routes for synthesis of the antidepressant compounds of this invention involve the reaction of a cycloalkenone or a cycloalkenone with an anion of an appropriately substituted phenylacetic acid, salt, ester, aldehyde or alcohol



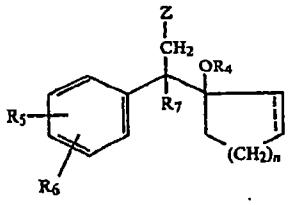
where B represents a carboxyl group or its salt or ester or a —CHO or CH_2OH functional group.

The carboxylic acid group may be converted to an acid halide, active ester or anhydride and directly reacted with the desired amine to yield, after reduction of the resulting amide, the end products of this invention. Also, the carboxylic acid group may be reduced with diisobutyl aluminum hydride or lithium aluminum hydride to obtain the corresponding aldehyde. The ester is readily converted to the aldehyde with diisobutyl aluminum hydride or to the alcohol with lithium aluminum hydride. The aldehyde may be condensed with hydroxylamine to afford the oxime —CH=NOH; with ammonium or a primary amine to afford an imine $—CH=NR_1$ or with a primary or secondary amine to afford



The alcohol $—CH_2OH$ may be converted to the corresponding nitro derivative by producing an organic sulfonate (mesyl ester) or halide followed by displacement with an inorganic nitrite. Reduction of these intermediates yields the primary amine intermediates or the secondary or tertiary amine end products of this invention. The alcohols may be converted to mesylates or tosylates, reacted with KCN to afford the nitrile, converted to the amide and subjected to a Hoffman rearrangement with bromine or chlorine and an alkali metal hydroxide.

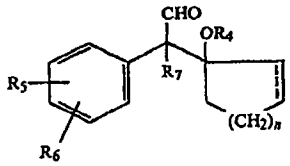
Additional routes to the desired products include the reaction of ammonia or HNR_1R_2 with



where Z is a leaving group such as a halogen or an organo sulfonyloxy (mesyl, tosyl and the like) group under conventional conditions. If desired, the amine reactant may be initially blocked with a relatively labile acyl group such as trifluoroacetyl to provide a reactant of the formula

prior to reaction with the alkylating reactant employing KOH and a very polar solvent such as dimethylsulfoxide, to provide a tertiary amide from which the acyl group may be readily removed to prepare the compound for non-symmetrical N-alkylation to insert R_2. Rather than N-alkylate, one may acylate or react the secondary amine with an aldehyde and subsequently reduce the amide or Schiff base. Similarly, reaction of the amine with an alkylchloroformate affords, upon reduction, an N-methylated amine. $LiAlH_4$ is a good reducing agent for these processes.

Reductive amination of the aldehyde



with ammonia, a primary amine or a secondary amine (Leuckart reaction) also yields the desired end products.

During the course of the synthesis of the end compounds of the invention by means of processes identified above, any hydroxy group represented by $-OR_4$, R_5 or R_6 may be in the free form or in the form of hydroxy protected by a removable protecting group, except of course, that the hydroxy group is not protected in any case where it is intended to participate in a reaction. The protected form is recommended where the hydroxy group may otherwise undergo an undesired reaction. Examples of protecting groups for hydroxy are given in Protective Groups in Organic Chemistry edited by J. F. W. McOmie, Chapters 3 and 4 (pages 95–182) published by Plenum Press (1973), and Protective Groups in Organic Chemistry by T. W. Greene, Chapters 2 and 3 (pages 10 to 113) published by John Wiley and Sons (1981). The protecting group may be removed at a suitable later stage in the synthesis. Similarly any amino or alkylamino group may be in a protected form where appropriate during the course of the *synthesis of the end compounds. Protecting groups for* amino are described in Chapter 2 (pages 43 to 94) of the McOmie book and Chapter 7 (pages 218 to 286) of the Greene book.

The end products contain either one or two asymmetric centers depending upon the saturated and unsaturated state of the cycloaliphatic ring, respectively. Individual stereoisomeric forms may be obtained or separated by standard procedures. For instance separation of the mixture in the case of an amine or carboxylic acid may be carried out by neutralisation with a suitable optically active compound to form salts which can be separated. Example 33 illustrates the typical resolution of the product of Example 3, Compound A.

The antidepressant activity of the end compounds of this invention was established by demonstrating that they (1) inhibit ^{3}H-imipramine binding in brain tissue when tested by a method analogous to that of Raisman et. al., Eur. J. Pharmacol. 61, 373–380 (1980); (2) inhibit synaptosomal uptake of norepinephrine (^{3}H-NE) and serotonin (^{14}C-5-HT) following the test procedure of Wood et. al., J. Neurochem. 37, 795–797 (1981); and antagonize reserpine induced hypothermia when tested in accordance with the procedure of Askew, Life Sci. 1, 725–730 (1963).

The results of these procedures affirmed the antidepressant activity of the end compounds of this invention in agreement with the most widely accepted theory of antidepressant activity and in correlation of activity with known tricyclic antidepressants. In at least two instances, namely, with the dimethylamino product of Example 3, and 4-chloro product in Example 11, the undesirable attribute of classical antidepressants observed as an anticholinergic property which is reflected by the inhibition of binding of the *muscarinic receptor* ligand, 3H-quinuclidinyl benzilate (QNB), and in the inhibition of carbachol-stimulated contraction of the guinea-pig ileum, is missing. Also missing is the attribute of classical antidepressants observed as an antihistaminic property which is reflected by the inhibition of the H_1 histamine receptor ligand, 3H-pyrilamine, and in the inhibition of histamine-stimulated contraction of the guinea-pig ileum.

As representative examples of the activity profile of the end compounds of this invention, the following data for testing of the dimethylamino product of Example 3, hereinafter Compound A, its oxazine variant, hereinafter Compound B, the 4-chloro product of Example 11, hereinafter referred to as Compound C, the 4-bromo product of Example 15, hereinafter referred to as Compound D, the 3-chloro product of Example 17, hereinafter referred to as Compound E, the 3-bromo product of Example 16, hereinafter referred to as Compound F, and the 3,4-dichloro product of Example 19, hereinafter referred to as Compound G, are presented as follows:

Inhibition of ^{3}H-imipramine binding: Compound A (HCl Salt) exhibited an inhibition constant (K_i) vs. ^{3}H-imipramine of 90 nM, making it a fairly potent ligand at this receptor site. Compound B was somewhat less potent, with a K_i of 350 nM. Compound C was virtually equipotent with Compound A, exhibiting a K_i vs. ^{3}H-imipramine of 100 nM. While not as potent as imipramine (K_i = 1.7 nM), these values fall in the range of desmethylimipramine (DMI) (K_i = 130 nM) and other tricyclic antidepressants. Atypical antidepressants (non-tricyclic) which have been tested, exhibit K_i's greater than 5000 nM in this assay. Compounds D, E, F and G exhibited inhibition constants of 62, 130, 52 and 37, respectively. Compounds A through G, representative of the other compounds of this invention, are thus comparable to known tricyclic antidepressants in this test

Inhibition of synaptosomal NE and 5-HT uptake: Results of the inhibition of NE and 5-HT synaptosomal uptake, expressed as the inhibitory concentration at which the rate of uptake was reduced to 50 percent (IC_{50}), are presented in the table below, where they are compared with the values for imipramine, DMI and amitriptyline:

Compound	IC_{50} (μM) NE	5-HT
Imipramine	0.26	0.12
DMI	0.15	3.0
Amitriptyline	0.50	0.60
Compound A	0.64	0.21
Compound B	4.7	2.9
Compound C	0.33	0.25
Compound D	0.21	0.11
Compound E	0.16	0.32
Compound F	0.11	0.23
Compound G	0.07	0.08

These results show that Compounds A and C to G are approximately equipotent to imipramine in NE and 5-HT uptake inhibition. Again, Compound B is somewhat less potent.

Inhibition of ^{3}H-QNB binding: In the QNB receptor binding assay, the Compounds A and C–G exhibited an IC_{50} greater than 10^{-5} molar and were therefore essentially inactive. Imipramine and DMI exhibit K_i's of 37 nM and 50 nM, respectively. These results suggest that, unlike the tricyclic antidepressants, Compounds A and C–G would have no muscarinic anticholinergic actions.

Inhibition of Carbachol-stimulated contraction of guinea-pig ileum: While imipramine at 1 μM exhibits a K_B of approximately 100 nM against carbachol-stimulated contraction of the guinea-pig ileum, Compound A was inactive at 1 μM. This result supports the suggestion of a lack of muscarinic anticholinergic action of Compound A.

Inhibition of ^{3}H-pyrilamine binding: While DMI exhibits a K_i versus ^{3}H-pyrilamine binding of 124 nM, Compound A was inactive. Compounds D–G exhibited an IC_{50} greater than 10^{-5} molar. These results suggest that, unlike tricyclic antidepressants, Compounds A and D–G have no antihistaminic property.

Inhibition of histamine-stimulated contraction of the guinea-pig ileum: Imipramine at 1 μM inhibits the histamine-stimulated contraction of the guinea-pig ileum with an approximate K_B of 8 nM. Compound A, in contrast, had no effect in this test at a concentration of 1 μM. This result supports the notion that Compound A has no antihistaminic action.

Antagonism of reserpine-induced hypothermia: The minimum effective dosage (M.E.D.) of compounds A through G established in antagonism of reserpine-induced hypothermia in mice (n=8 per group) in relation to desmethylimipramine (DMI) were:

Compound	Dose, mg/kg, i.p.
DMI	0.4
A	10.0 (and p.o.)
B	30.0
C	10.0
D	3.0
E	1.0
F	1.0
G	3.0

All mice received 5 mg/kg reserpine s.c. 18 h prior to test compound.

DMI, and Compounds A to G, are of approximately equal efficacy in the reversal of reserpine-induced hypothermia. Compound B was less potent than Compound A, Compound C was approximately equipotent with Compound A, Compounds D and G were approximately three times as potent as Compound A, and Compounds E and F were approximately ten times as potent as Compound A in the study.

Hence, the end compounds of this invention are useful in the treatment of depression, for which purpose they may be administered orally or parenterally in an amount sufficient to alleviate the symptoms of depression. The actual amount of antidepressant agent to be used will vary with the severity and nature of the depressed state, the animal being treated and the level of relief sought. In the human, an oral dose of from about 2 to about 50 milligrams, administered as needed represents appropriate posology. Intramuscular administration of from about 1 to about 25 milligrams provides a dosage comparable to that specified for oral administration. As with other antidepressants, therapy should be initiated with lower dosages and increased until the desired symptomatic relief is obtained.

Pharmaceutical compositions containing the antidepressant compounds of this invention represent an additional aspect of this invention. The active ingredient can be compounded into any of the usual oral dosage forms including tablets, capsules and liquid preparations such as elixirs and suspensions containing various colouring, flavouring, stabilizing and flavour masking substances. For compounding oral dosage forms, the active ingredient can be mixed with various conventional tabletting materials such as starch, calcium carbonate, lactose, sucrose and dicalcium phosphate to aid the tabletting or capsulating process. Magnesium stearate, as an additive, provides a useful lubricant function when desired.

The active ingredients can be dissolved or suspended in a pharmaceutically acceptable sterile liquid carrier, such as sterile water, sterile organic solvent or a mixture of both. Preferably a liquid carrier is one suitable for parenteral injection. Where the active ingredient is sufficiently soluble it can be dissolved in normal saline as a carrier; if it is too insoluble for this it can often be dissolved in a suitable organic solvent, for instance aqueous propylene glycol or polyethylene glycol solutions. Aqueous propylene glycol containing from 10 to 75% of the glycol by weight is generally suitable. In other instances other compositions can be made by dispersing the finely-divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution, or in a suitable oil, for instance arachis oil. Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by intramuscular, intraperitoneal or subcutaneous injection.

Preferably the pharmaceutical composition is in unit dosage form, e.g. as tablets or capsules. In such form, the composition is sub-divided in unit doses containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example, packeted powders or vials or ampoules. The unit dosage form can be a capsule, cachet or tablet itself, or

it can be the appropriate number of any of these in package form. The quantity of the active ingredient in a unit dose of composition may be varied or adjusted from 2 mg. or less to 50 mg. or more, according to the particular need and the activity of the active ingredient.

The following examples illustrate the preparative technique employed in production of the compounds of the invention.

EXAMPLE 1

1-[Cyano(p-methoxyphenyl)methyl]cyclohexanol

p-Methoxyphenylacetonitrile (50 gm, 0.3 mole) was added to dry tetrahydrofuran (250 ml) and the solution cooled to −70° C. under nitrogen. n-Butyl lithium in hexane (210 ml, 0.3 mole) was added dropwise, with stirring. The temperature was maintained below −50° C. and a yellow precipitate appeared. After the addition was complete, the reaction mixture was maintained below −50° C. for 30 minutes and cyclohexanone (35 ml, 0.3 mole) was added. After a further 45 minutes below −50° C. the temperature was allowed to rise to 0° C. and a saturated ammonium chloride solution was added. The layers were separated and the aqueous layer extracted with diethyl ether. The combined organic solution was washed with brine, dried over magnesium sulphate and evaporated. The product crystallized (25.2 gm, m.p. 125°-127° C.).

Mass Spectral Analysis: Molecular weight 245 [(M+1)+ by C.I.M.S.]

N.M.R. Analysis: δ 7.32, 6.95; (4H quartet, p-substituted aromatic) 3.8 (3H singlet, O—CH_3); 3.76 (1H, singlet, CH—CN); 1.56 (10H, multiplet, aliphatic cyclohexyl)ppm.

EXAMPLE 2

1-[2-amino-1-(p-methoxyphenyl)ethyl]cyclohexanol

1-[cyano(p-methoxyphenyl)methyl]cyclohexanol (12 g, 0.05 mole) was dissolved on warming in a mixture of ammonia-ethanol (20% v/v, 250 ml) and hydrogenated in a Parr apparatus over 5% rhodium on alumina (2.8 gm). The catalyst was filtered, washed well with ethanol and the combined filtrate evaporated and dried under vacuum yielding an oil (12 gm).

Mass Spectral Analysis: Molecular weight 249 (M+1)+ by C.I.M.S.

Thin Layer Chromatography: single spot, ninhydrin positive [chloroform-methanol-acetic acid (80:10:10 v/v)].

EXAMPLE 3

5-(4-methoxyphenyl)-3-methyl-3-aza-1-oxaspiro(5.5)-undecane and
1-[2-dimethyl-amino)-1-(4-methoxyphenyl)ethyl]cyclohexanol

1-[2-amino-1-(p-methoxyphenyl)ethyl]cyclohexanol (12 gm; 0.048 mole) was treated with a mixture of formaldehyde (11 ml), formic acid (14.5 ml, 88%) and water (125 ml) and heated at 100° C. for five hours. The reaction mixture was cooled and extracted with ethyl acetate. This extract was discarded. The aqueous residue was cooled in ice, rendered basic by the addition of solid potassium hydroxide, saturated with sodium chloride and thrice extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous potassium carbonate and evaporated to an oily residue (8 gm). This mixture of products was chromatographed on 1 kg of Mallinckrodt Silicar CC7 silica gel and the progress of the chromatography was monitored by thin layer chromatography using a system comprising ethanol:2N ammonia:ethyl acetate:cyclohexane 45:8:100:100 (v/v). Fractions containing the desired products were combined and the hydrochloride salts prepared using 4-N-isopropanolic HCl. The yields of the free bases were 1.4 gm (spiro compound) and 4.6 gm (dimethylamine) respectively.

COMPOUND B

5-(4-methoxyphenyl)-3-methyl-3-aza-1-oxaspiro(5.5)undecane

Melting Point: 242°-244° C.

Mass Spectral Analysis: Molecular weight 275 (M+1)+ by C.I.M.S.

N.M.R. Analysis: δ 7.22, 6.96 (4H quartet, p-substituted aromatic) 4.78 (2H quartet, O—CH_2—NCH_3) 3.8 (4H, O—CH_3, CH—CH_2—NCH_3) 3.3 (2H, multiplet CH—CH_2—NCH_3) 2.8 (3H, NCH_3) 0.9-1.8 (10H, broad multiplet, aliphatic cyclohexyl)ppm.

Compound A

1-[(2-dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol.

The hydrochloride: m.p. 215°-217° C.

Mass Spectral Analysis: Molecular weight 279 (M+1)+ by C.I.M.S. (free base).

N.M.R. Analysis: δ 7.32, 6.98 (4H quartet, p-substituted aromatic) 3.78 (3H, O—CH_3) 3.64 (2H, multiplet $CH_2N(CH_3)_2$) 3.06 (1H, multiplet CH—$CH_2(NCH_3)_2$) 2.74 (6H, $N(CH_3)_2$) 1.38 (10H, broad multiplet, alphatic cyclohexyl)ppm.

EXAMPLE 4

1-[1-(4-methoxyphenyl)-2-dimethylaminoethyl]cyclohexene

8.0 grams (0.029 moles) of 1-[1-(4-methoxyphenyl)-2-dimethylaminoethyl]cyclohexanol was dissolved in 300 ml of 2.0N aqueous hydrochloric acid and heated at reflux for 18 hours. It was allowed to cool, neutralized with 15% aqueous sodium hydroxide and extracted with chloroform. The chloroform extract was dried over sodium sulfate, filtered, and concentrated in vacuo to yield 7.0 grams of solid. This material was converted to the hydrochloride salt by treatment with 5N isopropanolic HCl and recrystallized a second time from isopropanol to yield 2.0 grams of the title compound as a white solid hydrochloride salt, m.p. 187°-189° C.

Analysis for: $C_{17}H_{26}ONCl$: Calculated: C, 69.23; H, 8.91; N, 4.75. Found: C, 69.39; H, 8.95; N, 4.95.

EXAMPLE 5

1-[(α-Aminomethyl)benzyl]-cyclohexanol

Phenylacetonitrile (10 g, 0.08 mole) was added to dry THF (100 ml) and the solution cooled to −70° C. under nitrogen. n-Butyllithium in hexane (64 ml, 0.1 mole) was added dropwise, the temperature being maintained below −40° C. and a yellow precipitate appeared. After addition the reaction mixture was maintained near −70° C. for 30 minutes and cyclohexanone (10 g, 0.1 mole) was added. After a further 45 minutes at −70° C. the temperature was allowed to rise to 0° C. and saturated ammonium chloride solution was added. The layers were separated and the aqueous layer extracted with diethyl ether. The combined organic solution was washed with brine, dried over magnesium sulphate and

evaporated. The product, 1-[α-cyanobenzyl]-cyclohexanol, crystallized (4.93 g, m.p. 100°–102° C.).

Mass Spectral Analysis: Molecular weight 215 (M+).

N.M.R. Analysis: δ 7.4 (5H singlet, aromatic 3.8 (1H, singlet, CH—CN) 1.6 (10H, multiplet aliphatic cyclohexyl)ppm.

A solution of 1-(α-cyanobenzyl)cyclohexanol (3.43 g, 0.02 mole) in a mixture of methanol and ammonia (9:1 v/v, 60 ml) was hydrogenated in a Parr apparatus over 5% rhodium on alumina (2 g). The catalyst was filtered and the filtrate evaporated. The residue was dissolved in ethyl acetate, washed with brine, dried over magnesium sulfate and evaporated. The hydrochloride m.p. 220°–222° (1.2 g) crystallized from diethyl ether-acetone.

Analysis for: $C_{14}H_{21}NO.HCl$: Calculated: C, 64.29; H, 8.67; N, 5.47%. Found: C, 65.74; H, 8.51; N, 5.56%.

N.M.R. Analysis (DMSO) δ 7.73 (5H singlet, aromatic) 3.46 (2H multiplet CH_2—NH_2), 3.0 (1H multiplet CH—CH_2NH_2) 0.9–1.7 (10H multiplet-aliphatic cyclohexyl) ppm.

Mass Spectral Analysis by Chemical Ionization: 220 $(M+H)^+$ (Mol. Wt. 219) (free base).

EXAMPLE 6

1-(α-[(Dimethylamino)methyl]benzyl)-cyclohexanol

1-[α-(aminomethyl)benzyl]cyclohexanol (1.38 g, 0.006 mole) was dissolved in a mixture of formaldehyde (2 ml) formic acid (2.6 ml) and water (25 ml), and refluxed at 95° C. for 18 hours. The reaction mixture was cooled, basified with solid KOH and extracted with methylene chloride. The extract was washed with brine, dried over magnesium sulphate and evaporated. The hydrochloride (m.p. 225°–227° C.) was prepared using 3N-isopropanolic HCl. Yield 589 mg.

Analysis for: $C_{16}H_{25}NO.HCl$: Calculated: C, 67.36; H, 9.12; N, 4.88%. Found: C, 67.7; H, 9.23; N, 4.93%.

Mass Spectral Analysis: Molecular weight 247 (M+. *free base*).

N.M.R. analysis: (DMSO) δ 7.4 (5H singlet, aromatic), 3.68 (2H, multiplet CH_2—N $(CH_3)_2$, 3.18 (1H, multiplet CH—CH_2N—$(CH_3)_2$ 2.68 (6H, $N(CH_3)_2$; 0.9–1.7 (10H multiplet aliphatic cyclohexyl)ppm.

EXAMPLE 7

1-(α-[(Methylamino)methyl]benzyl)cyclohexanol

1-[α-(aminomethyl)benzyl]cyclohexanol (1.59 g., 0.007 (mole) was dissolved in diethyl ether (10 ml.) and cooled to 5° C. Trifluoroacetic anhydride (2 g) was added and the mixture stirred at 0° C. for 30 minutes. The mixture was neutralized using saturated sodium bicarbonate solution and the layers separated. The organic layer was washed with brine, dried over magnesium sulphate and evaporated. A crystalline trifluoroacetamide m.p. 78°–80° C. was obtained (975 mg.).

The trifluoroacetamide (975 mg.) was dissolved in dry acetone (20 ml.) and treated with methyl iodide (2 g.). The solution was warmed to reflux temperature and dry powdered potassium hydroxide (1 g.) added, followed by excess methyl iodide. The mixture was refluxed for five minutes, then cooled and the acetone evaporated. Water (20 ml.) was added and the mixture refluxed for 15 minutes. It was cooled and extracted with ethyl acetate. The extract was washed with water and brine, dried over magnesium sulfate and evaporated to a crystalline product m.p. 92°–94° C. This was converted to the hydrochloride using 3N-isopropanolic HCl. Yield 235 mg., m.p. 208°–210° C.

N.M.R. Analysis ($CHCl_3$), δ 7.3 (7H, aromatic, HCl and $NH.CH_3$); 3.9 (1H multiplet CH—CH_2NH_2); 3.25 (2H multiplet CH_2—NH_2); 2.6 (3H singlet NH—CH_3); 0.8–1.9 (10H multiplet, aliphatic cyclohexyl)ppm.

Mass Spectral Analysis: Molecular weight by chemical ionization/M.S. 233 (M+1 at 234, free base).

EXAMPLE 8

1-(α-[(Dimethylamino)methyl]benzyl)cyclohexanol acetate

1-(α-[(Dimethylamino)methyl]benzyl)cyclohexanol, (0.5 g., 0.0025 mole) was treated with acetic anhydride (1 ml.) and pyridine (3 ml.) and the mixture stood at room temperature overnight. The reaction mixture was poured into water, basified with solid KOH and extracted with ethyl acetate. The extract was washed with water and brine, dried over magnesium sulphate and evaporated to an oil. After azetropic distillation with toluene to remove traces of pyridine, the oil was treated with 3N isopropanolic HCl and crystalline hydrochloride as the title compound was obtained (70 mg.) m.p. 163°–165° C.

NMR Analysis: ($CHCl_3$) δ 7.35 (5H singlet, aromatic); 4.2 (1H multiplet $CHCH_2N(CH_3)2$; 3.6 (2H multiplet CH_2—$N(CH_3)_2$); 2.65 (6H singlet, $N(CH_3)_2$); 2.1 (3H singlet, —O—C—CH_3): 0.9–1.7 (10H multiplet, aliphatic cyclohexyl)ppm.

Mass Spectral Analysis: Molecular weight 289 (M+, free base).

EXAMPLE 9

1-[cyano(p-chlorophenyl)methyl]cyclohexanol

By replacing the p-methoxyphenyl acetonitrile in Example 1 by a molar equivalent amount of p-chlorophenyl acetonitrile, there was obtained 1-cyano(p-chlorophenyl)methyl cyclohexanol (13.7 g.) m.p. 115°–117°.

Mass Spectral Analysis: Molecular weight 249 $(M+1)^+$ by C.I.M.S.

EXAMPLE 10

1-[2-amino-1-(4-chlorophenyl)ethyl]cyclohexanol

Lithium aluminum hydride (3.5 g.) was suspended in ice cold tetrahydrofuran (125 ml.) and concentrated sulphuric acid (2.5 ml.) added cautiously, with stirring. After one hour, 1-[cyano(p-chlorophenyl)methyl]cyclohexanol (15 g., 0.06 mole) was dissolved in tetrahydrofuran (100 ml.) and added rapidly dropwise with vigorous stirring and cooling. After a further two hours, a tetrahydrofuran-water mixture (1:1; 30 ml.) was added followed by 10% sodium hydroxide solution (50 ml.). The tetrahydrofuran was decanted and the residue washed well with diethyl ether and ethylacetate. The combined organic solution was dried over anhydrous potassium carbonate and evaporated to an oil (12 g.)

Mass Spectral Analysis: Molecular weight 253 $(M+1)^+$ by C.I.M.S.

EXAMPLE 11

1-[1-(4-chlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol

1-[2-amino-1-(4-chlorophenyl)ethyl]cyclohexanol (12 g., 0.04 mole) was treated with a mixture of formaldehyde (13.7 ml.) formic acid (18.1 ml.) and water (160

ml.) and refluxed at 100° C. for four hours. The reaction mixture was cooled extracted well with ethyl acetate and the extract discarded. The aqueous residue was cooled in ice and rendered basic by the addition of solid potassium hydroxide, saturated with sodium chloride and thrice extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous potassium carbonate and evaporated. A crystalline solid (3 g.) was filtered. It was converted to the hydrochloride salt using 4N-isopropanolic HCl; yielding 4.7 g., m.p. 241°–243° C.

Mass Spectral Analysis: Molecular Weight 281 $(M+1)^+$ by C.I.M.S.

NMR Analysis: δ 7.35 (4H singlet characteristic of 4chloro substitution) 3.65 (2H multiplet, CH_2—$CHN(CH_3)_2$), 3.0 (1H multiplet $CH_2CHN(CH_3)_2$ 1.4 (10H multiplet, aliphatic cyclohexyl)ppm.

EXAMPLE 12

1-[1-(4-methoxyphenyl)-2-(methylamino)ethyl]cyclohexanol

By replacing 1-[α-(aminomethyl)benzyl]cyclohexanol with a molar equivalent amount of 1-[2-amino-1-(p-methoxyphenyl)ethyl]cyclohexanol in Example 7, 1-[1-(4-methoxyphenyl)-2-methylamino)ethyl]cyclohexanol hydrochloride (m.p. 164°–166° C.) was obtained.

Mass Spectral Analysis: Molecular Weight 263 $(M+1)^+$ by C.I.M.S.

NMR Analysis: δ 7.28, 6.92 (4H quartet, p-substituted aromatic) 3.76 (3H singlet, OMe) 3.4 (2H multiplet, CH_2—$CHNCH_3)_2$ 2.9 (1H multiplet, $CH_2CHN(CH_3)_2$) 2.54 (3H, NCH_3) 1.4 (10H broad multiplet, aliphatic cyclohexyl)ppm.

EXAMPLE 13

4-bromo-N,N-dimethylbenzene acetamide

Para-bromophenylacetic acid (50 g., 0.233 mole) was dissolved in methylene chloride (500 ml) and treated with oxalyl chloride (23.3 ml., 0.27 mole) and D.M.F. (0.5 ml) at room temperature. The mixture was stirred for four hours until gas evolution ceased. The solvent was evaporated and the residue dried under vacuum to remove excess oxalyl chloride. The residue was dissolved in methylene chloride (300 ml) and treated with an excess of gaseous dimethylamine. The mixture was stirred overnight and the solvent evaporated. The residue was redissolved in methylene chloride and the solution washed with saturated sodium bicarbonate solution, N-hydrochloric acid, water, brine, dried over magnesium sulphate and evaporated. The buff-colored crystals were filtered with hexane and air-dried. Yield 51.2 g., m.p. 73°–76° C.

Analysis for: $C_{10}H_{12}NOBr$: Calculated: C, 49.59; H, 4.96; N, 5.79. Found: C, 48.98; H, 5.14; N, 5.77.

NMR Analysis ($CHCl_3$): δ 7.55 (4H quartet, aromatic) 3.65 (2H singlet) 2.95 (6H singlet, $N(CH_3)_2$)ppm.

EXAMPLE 14

1-[(4-bromophenyl)[(dimethylamino)carbonyl]methyl]-cyclohexanol

4-bromo-N,N-dimethylbenzene acetamide (15 g., 0.06 mole) was added to dry T.H.F. (250 ml) and the solution cooled to −78° C. under nitrogen. Straight chain butyl lithium in hexane (43.3 ml, 0.06 mole) was added dropwise, the temperature being maintained below −70° C. throughout. An orange coloured precipitate formed. After addition, the reaction mixture was maintained near −70° C. for 20 minutes and cyclohexanone (7.5 ml, 0.07 mole) was added. After a further 50 minutes at −78° C. the reaction mixture was poured into stirring saturated ammonium chloride solution. The layers were separated and the aqueous layer extracted with diethyl ether. The combined organic solution was washed with brine, dried over magnesium sulfate and evaporated. The product crystallised and was filtered with isopropanol (9.8 g., m.p. 140°–144° C.).

Analysis for: $C_{16}H_{22}NO_2Br$: Calculated: C, 56.47; H, 6.47; N, 4.12. Found: C, 57.22; H, 6.66; N, 4.21.

NMR Analysis ($CHCl_3$) δ 7.35 (4H, aromatic) 3.63 (1H singlet CH—$CON(CH_3)_2$) 2.95 (6H singlet, N—$(CH_3)_2$); 1.45 (10H multiplet, aliphatic cyclohexyl)ppm.

EXAMPLE 15

1-[1-(4-bromophenyl)-2-(dimethylamino)ethyl]cyclohexanol

Lithium aluminum hydride (0.7 g.) was suspended in dry THF (25 ml) cooled to 0° C. and concentrated sulfuric acid (0.5 ml) cautiously added in an in situ preparation of aluminum hydride. The mixture was stirred for one hour at 0° C. and the amide, 1-[(4-bromophenyl)[dimethylaminocarbonyl]methyl]cyclohexanol (4 g., 0.012 mole) was dissolved in THF (35 ml) and added rapidly dropwise. The reaction mixture was stirred at 0° C. for one hour. A THF-water mixture (1:1 v/v 6 ml) was added slowly followed by 10% sodium hydroxide (10 ml). The mixture was filtered and the residue washed well with ethyl acetate. The combined filtrate was dried over anhydrous potassium carbonate and evaporated to an oil (3.5 g) which was converted to the hydrochloride salt using 4N isopropanolic HCl.

Analysis for: $C_{16}H_{24}NOBr.HCl$: Calculated: C, 52.97; H, 6,9; N, 3.86. Found: C, 52.71; H, 6.63; N, 3.71.

NMR Analysis: (DMSO): δ 7.4 (4H, aromatic) 3.55 (2H doublet CH—$CH_2N(CH_3)_2$); 3.05 (1H, triplet, CH—$CH_2N(CH_3)_2$); 2.63 (6H singlet, N—$(CH_3)_2$) 1.30 (10H multiplet, aliphatic cyclohexyl)ppm.

EXAMPLE 16

1-[1-(3-bromophenyl)-2-dimethylamino)ethyl]cylohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of m-bromophenyl acetic acid in Example 13, and following procedures described in Examples 14 and 15, 1-[1-(3-bromophenyl)-2-(dimethylamino)ethyl]cyclohexanol was obtained as the hydrochloride, m.p. 198°–201° C.

Analysis for: $C_{16}H_{24}NOBr.HCl$: Calculated: C, 52.97; H, 6.90; N, 3,86. Found: C, 52.84; H, 6.92; N, 3.99.

EXAMPLE 17

1-[1-(3-chlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of m-chlorophenylacetic acid in Example 13, and following procedures described in Examples 14 and 15, 1-[1-(3-chlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol was obtained as the hydrochloride, m.p. 214°–216° C.

Analysis for: $C_{16}H_{24}NOCl.HCl$: Calculated: C, 60.38; H, 7.86; N, 4.4. Found: C, 60.07; H, 7.79; N, 3.93.

EXAMPLE 18

1-[1-(2-chlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of o-chlorophenylacetic acid in Example 13, and following procedures described in Examples 14 and 15, 1-[1-(2-chlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol was obtained as the hydrochloride, m.p. 205°–206° C.

Analysis for: $C_{16}H_{24}NOCl.HCl$: Calculated: C, 60.38; H, 7.86; N, 4.4. Found: C, 60.45; H, 7.71; N, 4.79.

EXAMPLE 19

1-[1-(3,4-dichlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of 3,4-dichlorophenylacetic acid in Example 13, and following procedures described in Examples 14 and 15, 1-[1-(3,4-dichlorophenyl-2-(dimethylamino)ethyl]cyclohexanol was obtained as the hydrochloride, m.p. 241°–244° C.

Analysis for: $C_{16}H_{23}NOCl_2.HCl$: Calculated: C, 54.47; H, 6.81; N, 3.97. Found: C, 54.8; H, 6.83; N, 3.99.

EXAMPLE 20

1-[1-(3,4-dichlorophenyl-2-(dimethylamino)ethyl]cyclohexanol

The product of the preceding example is similarly produced by the following procedure:

Lithium diisopropylamide was prepared by dissolving di-isopropylamine (69 ml) in THF (500 ml) followed by the addition of n-butyllithium (325 ml). After 10 minutes stirring, the straw colored liquid was cooled to −78° C. and a solution of the 3,4-dichloro-N,N-dimethylbenzeneacetamide (110.9 g, crude) was dissolved in 300 ml THF and added slowly. A dark red slurry was obtained. The mixture was stirred for a further 20 minutes and cyclohexanone (55.7 ml) was added. After 60 minutes at −78° C. the reaction mixture was poured into a saturated solution of ammonium chloride. The aqueous layer was extracted with diethyl ether and the combined organic solution was washed with brine, dried over K_2CO_3 and evaporated. The product, 1-[(3,4-dichlorophenyl) (dimethylaminocarbonyl)methyl]cyclohexanol, crystallized and was filtered. The crystals were washed with isopropanol and with petroleum ether and air dried. Yield: 73.6 g., m.p. 118°–120° C.

To an ice cold solution of Borane THF complex (152 ml, 152 mmole) was added a solution of 1-[(3,4-dichlorophenyl)(dimethylaminocarbonyl)methyl]cyclohexanol (30 g, 90 mmole) in THF. The mixture was refluxed for 2 hours and cooled again in an ice bath. 2N HCl (23 ml) was added and the mixture refluxed for 1.5 hours. It was cooled overnight. The reaction mixture was basified to pH 14 with solid potassium hydroxide and the layers were separated. The organic layer was washed with brine, dried over magnesium sulfate and evaporated to a solid. This was filtered and washed with diethyl ether and air dried. Yield: 15.4 g.; m.p. 128°–130° C.

This product was converted to the hydrochloride which was identical with the product in Example 19.

EXAMPLE 21

1-[2-(dimethylamino)-1-(3-methoxyphenyl)ethyl]cyclohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of m-methoxyphenyl acetic acid in Example 13, and following procedures described in Examples 14 and 15, 1-[2-(dimethylamino)-1-(3-methoxyphenyl)ethyl]cyclohexanol was obtained as the hydrochloride, m.p. 166°–168° C.

Analysis for: $C_{16}H_{25}NO_2.HCl$: Calculated: C, 64.11; H, 8.68; N, 4.67. Found: C, 63.12; H, 8.54; N, 4.46.

EXAMPLE 22

1-[1-(3,4-dimethoxyphenyl)-2-(dimethylamino)ethyl]-cyclohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of 3,4-dimethoxyphenyl acetic acid in Example 13, and following procedures described in Examples 14 and 15, 1-[1-(3,4-dimethoxyphenyl)-2-(dimethylamino)ethyl]cyclohexanol was obtained as the hydrochloride.

Analysis for: $C_{18}H_{29}NO_3.HCl$: Calculated: C, 62.88; H, 8.74; N, 4.08. Found: C, 62.42; H, 8.56; N, 3.98.

EXAMPLE 23

1-[2-(dimethylamino)-1-(4-trifluoromethylphenyl)ethyl]cyclohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of p-trifluoromethylphenyl acetic acid in Example 13, and following procedures described in Examples 14 and 15, 1-[2-(dimethylamino)-1-(4trifluoromethylphenyl)ethyl]cyclohexanol was obtained as the hydrochloride, m.p. 238°–240° C.

Analysis for: $C_{17}H_{25}NOF_3.HCl$: Calculated: C, 58.03; H, 7.16; N, 3.98. Found: C, 58.47; H, 7.16; N, 4.07.

EXAMPLE 24

1-[2-(dimethylamino)-1-(3-trifluoromethylphenyl)ethyl]cyclohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of m-trifluoromethylphenyl acetic acid in Example 13, and following procedures described in Examples 14 and 15, 1-[2-(dimethylamino)-1-(3-trifluoromethylphenyl)ethyl]cyclohexanol was produced as the hydrochloride, m.p. 194°–196° C.

Analysis for: $C_{17}H_{25}NOF_3.HCl$: Calculated: C, 58.03; H, 7.16; N, 3.98. Found: C, 58.31; H, 7.09; N, 4.09.

EXAMPLE 25

1-[2-(dimethylamino)-1-(4-methylphenyl)ethyl]cyclohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of p-methylphenyl acetic acid in Example 13, and following procedures described in Examples 14 and 15, 1-[2-(dimethylamino)-1-(4-methylphenyl)ethyl]cyclohexanol was produced as the hydrochloride.

Analysis for: $C_{17}H_{17}NO.HCl$: Calculated: C, 68.54; H, 9.17; N, 4.70. Found: C, 68.37; H, 9.31; N, 4.83.

EXAMPLE 26

1-[2-(dimethylamino)-1-(4-hydroxyphenyl)ethyl]cyclohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of p-benzyloxyphenyl acetic acid in Example 13, and following the procedures described in Examples 14 and 15, 1-[1-(4-benzyloxyphenyl)-2-(dimethylamino)ethyl]cyclohexanol was obtained.

Hydrogenolysis of this product to remove the benzyl protecting group from the 4-hydroxyphenyl moiety was accomplished by dissolving 1.0 grams of the product in 100 ml. ethanol. One gram, 10% Pd/C was introduced followed by cyclohexa-1,4-dienone (5 ml.). The mixture was stirred for ninety minutes at ambient temperature. The catalyst was removed by filtration and the solvent removed by evaporation to yield 800 mg. of solid. This solid 4-hydroxyphenyl product was converted to its fumarate salt via an acetone-ethanol solution, m.p. 140°–142° C.

Analysis for: $C_{16}H_{25}NO_2.C_4H_4O_4$: Calculated: C, 63.30; H, 7.70; N, 3.69. Found: C, 62.18; H, 7.90; N, 3.63.

EXAMPLE 27

1-[2-(dimethylamino)-1-(3-hydroxyphenyl)ethyl]cyclohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of m-benzyloxyphenyl acetic acid in Example 13, and following the procedures described in Examples 14 and 15, 1-[1-(3-benzyloxyphenyl)-2-(dimethylamino)ethyl]cyclohexanol was obtained.

Hydrogenolysis of this product (2.3 g) was conducted in 200 ml ethanol employing a Paar bomb, 300 mg. 10% Pd/C until uptake of hydrogen ceased. The catalyst was removed by filtration and the solvent evaporated to afford a solid product which was converted to its hydrochloride salt with 5N isopropanolic hydrochloride, m.p. 162°–164° C.

Analysis for: $C_{16}H_{25}NO_2.HCl$: Calculated: C, 64.08; H, 8.74; N, 4.67. Found: C, 62.78; H, 8.55; N, 4.55.

EXAMPLE 28

1-[1-(4-bromophenyl)-2-(dimethylamino)ethyl]cyclobutanol

By replacing cyclohexanone in Example 14 with a molar equivalent amount of cyclobutanone and following the procedure described in Example 15, 1-[1-(4-bromophenyl)-2-(dimethylamino)ethyl]cyclobutanol was obtained. It was converted to the hydrochloride salt, m.p. 220°–222° C.

Analysis for: $C_{14}H_{20}NOBr.HCl$: Calculated: C, 50.22; H, 6.28; N, 4.19. Found: C, 50.26; H, 6.11; N, 4.13.

EXAMPLE 29

1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclopentanol

By replacing p-bromophenylacetic acid with a molar equivalent amount of p-methoxyphenyl acetic acid in Example 13, 4-methoxy-N,N-dimethylbenzene acetamide was obtained. Subsequently, following the procedure outlined in Example 14, replacing cyclohexanone with a molar equivalent amount of cyclopentanone, there was obtained the corresponding cyclopentanol derivative. This intermediate was converted, following the procedure described in Example 15, to the title compound as the hydrochloride, m.p. 194° C.

Analysis for: $C_{16}H_{25}NO_2.HCl$: Calculated: C, 64.07; H, 8.76; N, 4.67. Found: C, 64.19; H, 8.72; N, 4.33.

EXAMPLE 30

1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cycloheptanol

By replacing cyclopentanone with a molar equivalent of cycloheptanone in Example 27, the title compound was obtained as the hydrochloride, m.p. 175°-177° C.

Analysis for: $C_{18}H_{29}NO_2.HCl.\frac{1}{4}H_2O$: Calculated: C, 65.03; H, 9.26; N, 4.21. Found: C, 65.25; H, 9.16; N, 4.29.

EXAMPLE 31

1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclooctanol

By replacing cyclopentanone with a molar equivalent amount of cyclooctanone in Example 29, the title compound was obtained as the hydrochloride, m.p. 178°–180° C.

Analysis for: $C_{19}H_{31}NO_2.HCl.\frac{1}{4}H_2O$: Calculated: C, 65.87; H, 9.48; N, 4.04. Found: C, 65.79; H, 9.08; N, 3.95.

EXAMPLE 32

1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohex-2-en-1-ol

By replacing 4-bromo-N,N-dimethylbenzeneacetamide with a molar equivalent of 4-methoxy-N,N-dimethylbenzeneacetamide in Example 14, and cyclohexanone with 2-cyclohexen-1-one, was obtained the corresponding cyclohexenone derivative. This intermediate was converted following the procedure described in Example 15 to the title compound as the fumarate, m.p. 128°–130° C.

Analysis for: $C_{17}H_{25}NO_2.C_4H_4O_4$: Calculated: C, 64.4; H, 7.31; N, 3.58. Found: C, 63.8; H, 7.46; N, 3.88.

EXAMPLE 33

Resolution of Racemic 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol

1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol (48.0 g., 0.173 m) dissolved in ethyl acetate (350 ml) was treated with di-p-toluoyl-d-tartaric acid (33.5 g., 0.082 m) dissolved in ethyl acetate (250 ml). After standing overnight, the solid was filtered. The solid was recrystallized three times by dissolving in boiling ethyl acetate (300 ml) and methanol (50 ml), concentrating by boiling to incipient crystallization and chilling. Yield 31.7 g., m.p. 126°-128° C. $[\alpha]_D^{25} = -50.51$; c=1.03 ethanol.

The salt was converted to its free base by shaking in 2N sodium hydroxide and diethyl ether. The ether layer was washed with brine, dried over anhydrous sodium carbonate, evaporated and dried in vacuo. yield 16.4 g., 68.5%. m.p. 104°-5° C. $[\alpha]_D^{25} = +27.95$; c=1.15, 95% ethanol.

The base was dissolved in ether (500 ml) and treated with 4.5N hydrogen chloride in isopropanol (20 ml). The resulting hydrochloride salt was recrystallized from warm methanol (75 ml) by dilution with ether (400 ml) and chilling. Yield 16.6 g. m.p. 239°-241° C. $[\alpha]_D^{25} = -4.38$; c=1.01, 95% ethanol.

The filtrate and washings from the original di-p-toluoyl-d-tartrate salt were evaporated to dryness. The free base was obtained by shaking the solid with 2N sodium hydroxide (400 ml), extracting with diethyl ether

(3×250 ml), washing the extracts with brine and drying. Yield 24.2 g. The base was dissolved in ethyl acetate (150 ml) and treated with di-p-toluoyl-l-tartaric acid (16.75 g, 0.0435 m) dissolved in ethyl acetate (150 ml). After standing overnight the salt was filtered and was recrystallized twice from ethyl acetate (300 ml) and methanol (50 ml) as described. Yield 29.4 g. m.p. 124°–127° C. $[\alpha]_D^{25}=+50.77$, c=0.845 ethanol.

The base was obtained in the manner described. Yield 14.7 g. m.p. 104°–105° C. $[\alpha]_D^{25}=-26.56$, c=1.22%, 95% ethanol.

The free base was converted to the hydrochloride salt. Yield 14.5 g. m.p. 239°–241° C. $[\alpha]_D^{25}=+4.98$, c=1.01, 95% ethanol.

EXAMPLE 34

1-[1-(4-aminophenyl)-2-dimethylaminoethyl]cyclohexanol

17.0 g (0.095 moles) of p-aminophenylacetic acid, dimethylamide was dissolved in 500 ml of tetrahydrofuran, placed under a nitrogen atmosphere, and cooled to −20° C. 23.6 g (1.15 equivalents) of 1,1,4,4-tetramethyl-1,4-dichlorosilylethylene was added, followed dropwise by a solution of 42 g (2.4 equivalents) of sodium bis(trimethylsilyl)amide in 250 ml of THF. The mixture was allowed to warm to room temperature and was stirred for 18 hours.

The mixture was next cooled to −78° C. and 71.6 ml (1.2 equivalents) of 1.6N n-butyl lithium in hexane added. The reaction was stirred for 45 minutes and then 20 ml (2.0 equivalents) of cyclohexanone added. The mixture was stirred for an additional 1 hour at −78° C. and then poured into a saturated aqueous solution of ammonium chloride. The organic phase was removed and the aqueous phase was extracted with diethyl ether. The combined organic phases were dried over sodium sulfate, filtered and concentrated in vacuo to yield 20 g of crude 1-[(4-aminophenyl)(dimethylaminocarbonyl)-methyl]cyclohexanol. Column chromatography on silica gel with 1% methanol in methylene chloride gave 16 g of essentially pure white solid. A sample twice recrystallized from ethanol had m.p. 169°–170° C. and the following elemental analysis:

Analysis for: $C_{16}H_{24}O_2N_2$: Calculated: C, 69.51; H, 8.77; N, 10.14. Found: C, 69.69; H, 8.96; N, 10.26.

5.0 g (0.018 mole) of the above amide was dissolved in 300 ml of dry tetrahydrofuran and added dropwise to a mixture of 1.1 g of lithium aluminum hydride and 8.0 ml of concentrated sulfuric acid in 200 ml of tetrahydrofuran at 0° C. The mixture was stirred at 0° C. for five hours, then the excess reagent was destroyed by the dropwise addition of 4 ml of 50:50 THF-water, then 4 ml of 15% aqueous sodium hydroxide and finally 4 ml of water. The mixture was filtered and the precipitate washed several times with THF. The combined filtrates were evaporated and the residue recrystallized from isopropanol to give 3.8 g of the title compound as the free base. Treatment with excess oxalic acid in ethyl acetate gave the dioxalate, m.p. 105° C.(d).

Analysis for: $C_{20}H_{30}N_2O_9$: Calculated: C, 54.28; H, 6.84; N, 6.33. Found: C, 53.96; H, 6.83; N, 6.24.

EXAMPLE 35

1-[1-(4-nitrophenyl)-2-dimethylaminoethyl]cyclohexanol

2.0 g (7.6 mmoles) of 1-[1-(4-aminophenyl)-2-dimethylaminoethyl]cyclohexanol was dissolved in 50 ml of methylene chloride and added dropwise to a stirring solution of 2.2 g (2.5 equivalents) of nitrosonium tetrafluoroborate. The reaction was stirred at room temperature for four hours. The methylene chloride was then removed in vacuo and replaced with 100 ml of water. This solution was added slowly to a mixture of 2.0 g of copper in 200 ml of 1N sodium nitrite and the combination stirred for 2 hours at room temperature. Extraction with methylene chloride, drying, and evaporation in vacuo yielded 2.0 g of the free base of the title compound. Recrystallization from isopropanolic HCl gave the hydrochloride, m.p. 211°–212° C.

Analysis for: $C_{16}H_{24}O_3N_2$: Calculated: C, 58.42; H, 7.37; N, 8.52. Found: C, 58.03; H, 7.53; N, 8.69.

EXAMPLE 36

1-[2-dimethylamino)-1-(3-bromo-4-methoxyphenyl)ethyl]cyclohexanol

By replacing 1-[2-amino-1-(p-methoxyphenyl)ethyl]-cyclohexanol in Example 3 with a molar equivalent amount of 1-[2-amino-1-(3-bromo-4-methoxyphenyl)ethyl]cyclohexanol and refluxing overnight, the title compound was obtained, m.p. 218°–220° C.

Analysis for: $C_{17}H_{26}NO_2Br.HCl$: Calculated: C, 57.98; H, 6.92; N, 3.56. Found: C, 51.57; H, 6.79; N, 3.46.

EXAMPLE 37

1-[2-[1-(dimethylamino)-2-(4-methoxyphenyl)propyl]-]cyclohexanol

14.7 g (0.10 mole) of p-methoxyphenylacetonitrile was dissolved in 250 ml of dry tetrahyrofuran and placed in a dry ice/isopropanol bath under N_2. 69.0 ml of 1.6M n-butyl lithium (0.11 mole) was added dropwise over 30 minutes and the mixture stirred at −78° C. for one hour. The lithium salt of the nitrile precipitated as a yellow solid during this time. 71.0 g (0.50 mole) of methyl iodide was then added and stirring at −78° C. continued for an additional hour. The mixture was then poured into saturated ammonium chloride and the product extracted into diethyl ether, washed with saturated sodium chloride and dried over sodium sulfide. It was filtered and evaporated, redissolved in methylene chloride and passed through Florisel ®. Evaporation gave 15.0 g of α-(p-methoxyphenyl)propionitrile as an orange oil.

The α-(p-methoxyphenyl)propionitrile prepared above was redissolved in 250 ml of tetrahydrofuran and cooled to −78° C. in dry ice/isopropanol. 69.0 ml of 1.6M n-butyllithium was added over 30 minutes and the mixture stirred for 1 hour under nitrogen. 20 ml of cyclohexanone was then added and stirring at 078° C. was continued for an additional hour. The mixture was poured into saturated ammonium chloride solution and the product extracted with diethyl ether. It was washed with water, saturated sodium chloride and dried over sodium sulfate. Filtration and evaporation gave 21.5 g of white solid. A sample twice recrystallized from benzene had m.p. 129° C. and the following analysis:

Analysis for: $C_{16}H_{21}NO_2$: Calculated: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.95; H, 8.04; N, 5.29.

4.0 g (15 mmoles) of the β-hydroxynitrile prepared above was dissolved in 200 ml of tetrahydrofuran and 50 ml of 1M borane tetrahydrofuran complex was added. The mixture was refluxed for 2 hours and allowed to cool. 200 ml of 2N HCl was added and the THF removed in vacuo. The aqueous solution was made basic by the addition of solid pottasium carbonate

and the product extracted with 500 ml of ethyl acetate, washed with saturated sodium chloride and dried over sodium sulfate. This was filtered and evaporated and treated with isopropanolic HCl and diethyl ether to yield 3.3 g of the primary amine, m.p. 209° C.

Analysis for: $C_{16}H_{26}NO_2Cl$: Calculated: C, 64.09; H, 8.74; N, 4.67. Found: C, 63.70; H, 8.60; N, 4.59.

3.0 g (10 mmole) of the primary amine hydrochloride was dissolved in 200 ml of absolute ethanol. 5.0 ml of 37% aqueous formaldehyde and 1.0 g of 10% palladium on carbon were added and the mixture was treated with 50 psi of hydrogen on a Parr shaker for 3 days. The mixture was then filtered and evaporated and the solvent replaced with 300 ml of water and washed with 300 ml of ethyl acetate. The aqueous solution was then made pasic with solid sodium carbonate and again extracted with ethyl acetate. The organic extract was washed with saturated brine and dried over sodium sulfate. It was filtered and evaporated and the title compound precipitated as the hydrochloride from isopropanol/ether by the addition of isopropanolic HCl. A second crystallization from isopropanol gave 2.0 g of white solid, m.p. 271° C.

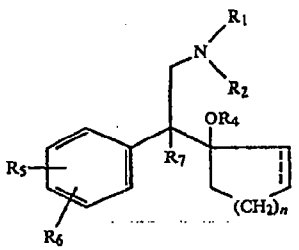
Analysis for: $C_{18}H_{30}NO_2Cl$: Calculated: C, 65.93; H, 9.22; N, 4.27. Found: C, 65.73; H, 8.93; N, 4.20.

EXAMPLE 38

By following a procedure similar to Examples 13 to 15, using (a) 3,4-dibromophenylacetic acid, (b) 3-methylphenylacetic acid, (c) 4-bromophenylacetic acid and (d) 3-methoxyphenylacetic acid instead of p-bromophenylacetic acid and, as the cycloalkanone, (a) cyclohexanone, (b) cyclohexanone, (c) cyclobutanone and (d) cyclopentanone, there are prepared (a) 1-[1-(3,4-dibromophenyl)-2-(dimethylamino)ethyl]cyclohexanol, (b) 1-[2-(dimethylamino)-1-(3-methylphenyl)ethyl]cyclohexanol, (c) 1-[1-(4-bromophenyl)-2-(dimethylamino)ethyl]cyclobutanol and (d) 1-[2-(dimethylamino)-1-(3-methoxyphenyl)ethyl]cyclopentanol.

What is claimed is:

1. A compound of the formula:



wherein

the dotted line represents optional olefinic unsaturation, and

R_1 is hydrogen or alkyl of 1 to 6 carbon atoms;

R_2 is alkyl of 1 to 6 carbon atoms;

R_4 is hydrogen, alkyl of 1 to 6 carbon atoms, formyl, or alkanoyl of 2 to 7 carbon atoms;

R_5 and R_6 are independently hydrogen, hydroxyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, nitro, alkylmercapto of 1 to 6 carbon atoms, amino, alkylamino of 1 to 6 carbon atoms, dialkylamino in which each alkyl group is of 1 to 6 carbon atoms, alkanamido of 2 to 7 carbon atoms, halo, or trifluoromethyl;

R_7 is hydrogen or alkyl of 1 to 6 carbon atoms; and

n is one of the integers 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1 in which in which R_1 is hydrogen or alkyl of 1 to 3 carbon atoms; R_2 is alkyl of 1 to 3 carbon atoms; R_5 is hydrogen, alkoxy of 1 to 3 carbon atoms, chloro, bromo, trifluoromethyl or alkyl of 1 to 3 carbon atoms; R_6 is alkyl of 1 to 3 carbon atoms, alkoxy of 1 to 3 carbon atoms, chloro, bromo, trifluoromethyl or alkanoyloxy of 2 to 3 carbon atoms; R_7 is hydrogen or alkyl of 1 to 3 carbon atoms; or a pharmaceutically acceptable salt thereof.

3. A compound of claim 2 in which R_5 and R_6 are in meta or para positions and n is 2.

4. The compound of claim 1 which is 1-[(2-dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

5. The compound of claim 1 which is 1-(α-[(dimethylamino)methyl]benzyl)cyclohexanol or a pharmaceutically acceptable salt thereof.

6. The compound of claim 1 which is 1-(α-[methylamino)methyl]benzyl)cyclohexanol or a pharmaceutically acceptable salt thereof.

7. The compound of claim 1 which is 1-[1-(4-chlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

8. The compound of claim 1 which is 1-[1-(4-methoxyphenyl)-2-(methylamino)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

9. The compound of claim 1 which is 1-[1-(4-bromophenyl-2-(dimethylamino)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

10. The compound of claim 1 which is 1-[1-(3-bromophenyl)-2-(dimethylamino)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

11. The compound of claim 1 which is 1-[1-(3-chlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

12. The compound of claim 1 which is 1-[1-(2-chlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

13. The compound of claim 1 which is 1-[1-(3,4-dichlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

14. The compound of claim 1 which is 1-[2-[1-(dimethylamino)-2-(4-methoxyphenyl)propyl]]cyclohexanol or a pharmaceutically acceptable salt thereof.

15. The compound of claim 1 which is 1-[2-(dimethylamino)-1-(3-methoxyphenyl)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

16. The compound of claim 1 which is 1-[1-(3,4-dimethoxyphenyl)-2-(dimethylamino)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

17. The compound of claim 1 which is 1-[2-(dimethylamino)-1-(4-trifluoromethylphenyl)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

18. The compound of claim 1 which is 1-[2-(dimethylamino)-1-(3-trifluoromethylphenyl)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

19. The compound of claim 1 which is 1-[2-(dimethylamino)-1-(4-methylphenyl)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

20. The compound of claim 1 which is 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohex-2-en-1-ol or a pharmaceutically acceptable salt thereof.

21. The compound of claim 1 which is 1-[2-(dimethylamino)-1-(4-hydroxyphenyl)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

22. The compound of claim 1 which is 1-[2-(dimethylamino)-1-(3-hydroxyphenyl)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

23. The compound of claim 1 which is 1-[1-(4-aminophenyl)-2-(dimethylamino)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

24. The compound of claim 1 which is 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclopentanol or a pharmaceutically acceptable salt thereof.

25. The compound of claim 1 which is 1-[1-(4-nitrophenyl)-2-(dimethylamino)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

26. The compound of claim 1 which is 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cycloheptanol or a pharmaceutically acceptable salt thereof.

27. The compound of claim 1 which is 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclooctanol or a pharmaceutically acceptable salt thereof.

28. The compound of claim 1 which is 1-[2-(dimethylamino)-1-(3-bromo-4-methoxyphenyl)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

29. The compound of claim 1 which is 1-[1-(3,4-dibromophenyl)-2-(dimethylamino)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

30. The compound of claim 1 which is 1-[(2-dimethylamino)-1-(3-methylphenyl)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

31. The compound of claim 1 which is 1-[1-(4-bromophenyl-2-(dimethylamino)ethyl]cyclobutanol or a pharmaceutically acceptable salt thereof.

32. The compound of claim 1 which is 1-[2-(dimethylamino)-1-(3-methoxyphenyl)ethyl]cyclopentanol or a pharmaceutically acceptable salt thereof.

* * * * *

EXHIBITS 2 – 10
REDACTED

Exhibit 11

US006274171B1

(12) **United States Patent**
Sherman et al.

(10) **Patent No.: US 6,274,171 B1**
(45) **Date of Patent: Aug. 14, 2001**

(54) **EXTENDED RELEASE FORMULATION OF VENLAFAXINE HYDROCHLORIDE**

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(21) Appl. No.: **09/488,629**

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Related U.S. Application Data

(63) Continuation-in-part of application No. 08/964,328, filed on Nov. 5, 1997, now abandoned, which is a continuation-in-part of application No. 08/821,137, filed on Mar. 20, 1997, now abandoned.

(60) Provisional application No. 60/014,006, filed on Mar. 25, 1996.

(51) **Int. Cl.**[7] **A61K 9/52**; A61K 9/54; A61K 9/62

(52) **U.S. Cl.** **424/461**; 424/457; 424/458; 424/459; 514/781; 514/962

(58) **Field of Search** 424/495, 494, 424/461, 458, 459, 457, 456, 462

(56) **References Cited**

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(57) **ABSTRACT**

This invention relates to a 24 hour extended release dosage formulation and unit dosage form thereof of venlafaxine hydrochloride, an antidepressant, which provides better control of blood plasma levels than conventional tablet formulations which must be administered two or more times a day and further provides a lower incidence of nausea and vomiting than the conventional tablets. More particularly, the invention comprises an extended release formulation of venlafaxine hydrochloride comprising a therapeutically effective amount of venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and, optionally, hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose.

25 Claims, No Drawings

EXTENDED RELEASE FORMULATION OF VENLAFAXINE HYDROCHLORIDE

This application continuation-in-part of Application Ser. No. 08/964,328, filed Nov. 5, 1997 abandoned, which is a continuation-in-part of Application Ser. No. 08/821,137, filed Mar. 20, 1997 abandoned, which, in turn, claims priority from Provisional Application No. 60/014,006 filed Mar. 25, 1996.

BACKGROUND OF THE INVENTION

Extended release drug formulations are conventionally produced as compressed tablets by hydrogel tablet technology. To produce these sustained release tablet drug dosage forms, the active ingredient is conventionally compounded with cellulose ethers such as methyl cellulose, ethyl cellulose or hydroxypropylmethylcellulose with or without other excipients and the resulting mixture is pressed into tablets. When the tablets are orally administered, the cellulose ethers in the tablets swell upon hydration from moisture in the digestive system, thereby limiting exposure of the active ingredient to moisture. As the cellulose ethers are gradually leached away by moisture, water more deeply penetrates the gel matrix and the active ingredient slowly dissolves and diffuses through the gel, making it available for absorption by the body. An example of such a sustained release dosage form of the analgesic/anti-inflammatory drug etodolac (Lodine®) appears in U.S. Pat. No. 4,966,768. U.S. Pat. No. 4,389,393 discloses sustained release therapeutic compressed solid unit dose forms of an active ingredient plus a carrier base comprised of a high molecular weight hydroxypropylmethylcellulose, methyl cellulose, sodium carboxymethylcellulose and or other cellulose ether.

Where the production of tablets is not feasible, it is conventional in the drug industry to prepare encapsulated drug formulations which provide extended or sustained release properties. In this situation, the extended release capsule dosage forms may be formulated by mixing the drug with one or more binding agents to form a uniform mixture which is then moistened with water or a solvent such as ethanol to form an extrudable plastic mass from which small diameter, typically 1 mm, cylinders of drug/matrix are extruded, broken into appropriate lengths and transformed into spheroids using standard spheronization equipment. The spheroids, after drying, may then be film-coated to retard dissolution. The film-coated spheroids may then be placed in pharmaceutically acceptable capsules, such as starch or gelatin capsules, in the quantity needed to obtain the desired therapeutic effect. Spheroids releasing the drug at different rates may be combined in a capsule to obtain desired release rates and blood levels. U.S. Pat. No. 4,138,475 discloses a sustained release pharmaceutical composition consisting of a hard gelatin capsule filled with film-coated spheroids comprised of propanolol in admixture with microcrystalline cellulose wherein the film coating is composed of ethyl cellulose, optionally, with hydroxypropylmethylcellulose and/or a plasticizer.

Venlafaxine, 1-[2-dimethylamino)-1-(4-methoxyphenyl) ethyl]cyclohexanol, is an important drug in the neuropharmacological arsenal used for treatment of depression. Venlafaxine and the acid addition salts thereof are disclosed in U.S. Pat. No. 4,535,186. Venlafaxine hydrochloride is presently administered to adults in compressed tablet form in doses ranging from 75 to 350 mg/day, in divided doses two or three times a day. In therapeutic dosing with venlafaxine hydrochloride tablets, rapid dissolution results in a rapid

increase in blood plasma levels of the active compound shortly after administration followed by a decrease in blood plasma levels over several hours as the active compound is eliminated or metabolized, until subtherapeutic plasma levels are approached after about twelve hours following administration, thus requiring additional dosing with the drug. With the plural daily dosing regimen, the most common side effect is nausea, experienced by about forty five percent of patients under treatment with venlafaxine hydrochloride. Vomiting also occurs in about seventeen percent of the patients.

BRIEF DESCRIPTION OF THE INVENTION

In accordance with this invention, there is provided an extended release (ER), encapsulated formulation containing venlafaxine hydrochloride as the active drug s component, which provides in a single dose, a therapeutic blood serum level over a twenty four hour period.

Through administration of the venlafaxine formulation of this invention, there is provided a method for obtaining a flattened drug plasma concentration to time profile, thereby affording a tighter plasma therapeutic range control than can be obtained with multiple daily dosing. In other words, this invention provides a method for eliminating the sharp peaks and troughs (hills and valleys) in blood plasma drug levels induced by multiple daily dosing with conventional immediate release venlafaxine hydrochloride tablets. In essence, the plasma levels of venlafaxine Is hydrochloride rise, after administration of the extended release formulations of this invention, for between about five to about eight hours (optimally about six hours) and then begin to fall through a protracted, substantially linear decrease from the peak plasma level for the remainder of the twenty four hour period, maintaining at least a threshold therapeutic level of the drug during the entire twenty-four period. In contrast, the conventional immediate release venlafaxine hydrochloride tablets give peak blood plasma levels in 2 to 4 hours. Hence, in accordance with the use aspect of this invention, there is provided a method for moderating the plural blood plasma peaks and valleys attending the pharmacokinetic utilization of multiple daily tablet dosing with venlafaxine hydrochloride which comprises administering to a patient in need of treatment with venlafaxine hydrochloride, a one-a-day, extended release formulation of venlafaxine hydrochloride.

The use of the one-a-day venlafaxine hydrochloride formulations of this invention reduces by adaptation, the level of nausea and incidence of emesis that attend the administration of multiple daily dosing. In clinical trials of venlafaxine hydrochloride ER, the probability of developing nausea in the course of the trials was greatly reduced after the first week. Venlafaxine ER showed a statistically significant improvement over conventional venlafaxine hydrochloride tablets in two eight-week and one 12 week clinical studies. Thus, in accordance with this use aspect of the invention there is provided a method for reducing the level of nausea and incidence of emesis attending the administration of venlafaxine hydrochloride which comprises dosing a patient in need of treatment with venlafaxine hydrochloride with an extended release formulation of venlafaxine hydrochloride once a day in a therapeutically effective amount.

The formulations of this invention comprise an extended release formulation of venlafaxine hydrochloride comprising a therapeutically effective amount of venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and, optionally,

hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose. Unless otherwise noted, the percentage compositions mentioned herein refer to percentages of the total weight of the final composition or formulation.

More particularly, the extended release formulations of this invention are those above wherein the spheroids are comprised of from about 6% to about 40% venlafaxine hydrochloride by weight, about 50% to about 95% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

A preferred embodiment of this invention are formulations wherein the spheroids are comprised of about 30% to about 40% venlafaxine hydrochloride by weight, about 50% to about 70% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

Another preferred lower dose formulation of this invention are those wherein the spheroids are comprised less than 30% venlafaxine hydrochloride. These formulations comprise spheroids of from about 6% to about 30% venlafaxine hydrochloride by weight, about 70% to about 94% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

Within this subgroup of lower dose formulations are formulations in which the spheroids are comprised of from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. Another preferred subgroup of spheroids in these formulations comprises from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. A further preferred subgroup of spheroids in these formulations comprises from about 6% to about 20% venlafaxine hydrochloride and from about 94% to about 80% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. Within each of these subgroups is understood to be formulations in which the spheroids are comprised of venlafaxine HCl and microcrystalline cellulose in the amounts indicated, with no hydroxypropylmethylcellulose present. Each of these formulations is also preferably contained in a gelatin capsule, preferably a hard gelatin capsule.

DETAILED DESCRIPTION OF THE INVENTION

1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride is polymorphic. Of the forms isolated and characterized to date, Form I is considered to be the kinetic product of crystallization which can be converted to Form II upon heating in the crystallization solvent. Forms I and II cannot be distinguished by their melting points but do exhibit some differences in their infrared spectra and X-ray diffraction patterns. Any of the polymorphic forms such as Form I or Form II may be used in the formulations of the present invention.

The extended release formulations of this invention are comprised of 1-[2-(dimethylamino)-1-(4-methoxyphenyl) ethyl]cyclohexanol hydrochloride in admixture with microcrystalline cellulose and hydroxypropylmethylcellulose. Formed as beads or spheroids, the drug containing formulation is coated with a mixture of ethyl cellulose and hydroxypropylmethyl cellulose to provide the desired level of coating, generally from about two to about twelve percent on a weight/weight basis of final product or more preferably from about five to about ten percent (w/w), with best results obtained at from about 6 to about 8 percent (w/w). More specifically, the extended release spheroid formulations of this invention comprise from about 30 to 40 percent venlafaxine hydrochloride, from about 50 to about 70 percent microcrystalline cellulose, NF, from about 0.25 to about I percent hydroxypropylmethylcellulose, USP, and from about 5 to about 10 percent film coating, all on a weight/weight basis. And preferably, the spheroid formulations contain about 35 percent venlafaxine hydrochloride, about 55 to 60 percent microcrystalline cellulose NF (Avicel® PH101), about one half percent hydroxypropylmethylcellulose 2208 USP (K3, Dow, which has a viscosity of 3 cps for 2% aqueous solutions, a methoxy content of 19–24% and a hydroxypropoxy content of 4–13%), and from about 6 to 8 percent film coating.

The film coating is comprised of 80 to 90 percent of ethyl cellulose, NF and 10 to 20 percent hydroxypropylmethylcellulose (2910), USP on a weight/weight basis. Preferably the ethyl cellulose has a ethoxy content of 44.0–51% and a viscosity of 50 cps for a 5% aqueous solution and the hydroxypropylmethylcellulose is USP 2910 having a viscosity of 6 cps at 2% aqueous solution with a methoxy content of 28–30% and a hydroxypropoxy content of 7–12%. The ethyl cellulose used herein is Aqualon HG 2834.

Other equivalents of the hydroxypropylmethylcelluloses 2208 and 2910 USP and ethyl cellulose, NF, having the same chemical and physical characteristics as the proprietary products named above may be substituted in the formulation without changing the inventive concept. Important characteristics of suitable hydroxypropylmethylcelluloses include a low viscosity, preferably less than 10 cps and more preferably 2–5 cps, and a gel temperature above that of the temperature of the extrudate during extrusion. As explained below, these and other characteristics which enable the extrudate to remain moist and soft (pliable) are preferred for the hydroxypropylmethylcellulose. In the examples below, the extrudate temperature was generally 50–55° C.

It was completely unexpected that an extended release formulation containing venlafaxine hydrochloride could be obtained because the hydrochloride of venlafaxine proved to be extremely water soluble. Numerous attempts to produce extended release tablets by hydrogel technology proved to be fruitless because the compressed tablets were either physically unstable (poor compressibility or capping problems) or dissolved too rapidly in dissolution studies. Typically, the tablets prepared as hydrogel sustained release formulations gave 40–50% dissolution at 2 hrs, 60–70% dissolution at 4 hrs and 85–100% dissolution at 8 hrs.

Numerous spheroid formulations were prepared using different grades of microcrystalline cellulose and hydroxypropylmethylcellulose, different ratios of venlafaxine hydrochloride and filler, different binders such as polyvinylpyrrolidone, methylcellulose, water, and polyethylene glycol of different molecular weight ranges in order to find a formulation which would provide a suitable granulation mix which could be extruded properly. In the extrusion process, heat buildup occurred which dried out the extrudate so much that it was difficult to convert the extruded cylinders into spheroids. Addition of hydroxypropylmethylcellulose 2208 to the venlafaxine hydrochloride-microcrystalline cellulose mix made production of spheroids practical.

The encapsulated formulations of this invention may be produced in a uniform dosage for a specified dissolution profile upon oral administration by techniques understood in the art. For instance, the spheroid components may be blended for uniformity with a desired concentration of active ingredient, then spheronized and dried. The resulting spheroids can then be sifted through a mesh of appropriate pore size to obtain a spheroid batch of uniform and prescribed size.

The resulting spheroids can be coated and resifted to remove any agglomerates produced in the coating steps. During the coating process samples of the coated spheroids may be tested for their distribution profile. If the dissolution occurs too rapidly, additional coating may be applied until the spheroids present a desired dissolution rate.

The following examples are presented to illustrate applicant's solution to the problem of preparation of the extended release drug containing formulations of this invention.

EXAMPLE NO. 1

Venlafaxine Hydrochloride Extended Release Capsules

A mixture of 44.8 parts (88.4% free base) of venlafaxine hydrochloride, 74.6 parts of the microcrystalline cellulose, NF, and 0.60 parts of hydroxypropylmethyl cellulose 2208, USP, are blended with the addition of 41.0 parts water. The plastic mass of material is extruded, spheronized and dried to provide uncoated drug containing spheroids.

Stir 38.25 parts of ethyl cellulose, NF, HG2834 and 6.75 parts of hydroxypropylmethylcellulose 2910, USP in a 1:1 v/v mixture of methylene chloride and anhydrous methanol until solution of the film coating material is complete.

To a fluidized bed of the uncoated spheroids is applied 0.667 parts of coating solution per part of uncoated spheroids to obtain extended release, film coated spheroids having a coating level of 3%.

The spheroids are sieved to retain the coated spheroids of a particle size between 0.85 mm to 1.76 mm diameter. These selected film coated spheroids are filled into pharmaceutically acceptable capsules conventionally, such as starch or gelatin capsules.

EXAMPLE NO. 2

Same as for Example 1 except that 1.11 parts of the film coating solution per part of uncoated spheroids is applied to obtain a coating level of 5%.

EXAMPLE NO. 3

Same as for Example 1 except that 1.33 parts of the film coating solution is applied to 1 part of uncoated spheroids to obtain a coating level of 6%.

EXAMPLE NO. 4

Same as for Example 1 except that 1.55 parts of the film coating solution is applied to 1 part of uncoated spheroids to obtain a coating level of 7%.

In the foregoing failed experiments and in Examples 1–4, the extrusion was carried out on an Alexanderwerk extruder. Subsequent experiments carried out on Hutt and Nica extruders surprisingly demonstrated that acceptable, and even improved, spheroids could be made without the use of an hydroxypropylmethylcellulose.

In such further experiments the applicability of the invention was extended to formulations wherein the weight percentage of venlafaxine hydrochloride is 6% to 40%, preferably 8% to 35%. Thus, the extended release spheroid formulations of this invention comprise from about 6 to about 40 percent venlafaxine hydrochloride, from about 50 to about 94 percent microcrystalline cellulose, NF, optionally, from about 0.25 to about 1 percent hydroxypropylmethylcellulose, and from about 2 to about 12 percent, preferably about 3 to 9 percent, film coating.

Spheroids of the invention were produced having 8.25% (w/w) venlafaxine hydrochloride and the remainder (91.75%, w/w) being microcrystalline cellulose, with a coating of from 3 to 5% (w/w), preferably 4%, of the total weight. The spheroids with 8.25% venlafaxine hydrochloride and 4% coating were filled into No. 2 white opaque shells with a target fill weight of 236 mg.

Further spheroids of the invention were produced having 16.5% (w/w) venlafaxine hydrochloride and the remainder (83.5%,w/w) being microcrystalline cellulose, with a coating of from 4 to 6% (w/w), preferably 5%, of the total weight. The spheroids 16.5% venlafaxine hydrochloride and 5% coating were filled into No. 2 white opaque shells with a target fill weight of 122 mg.

The test for acceptability of the coating level is determined by analysis of the dissolution rate of the finished coated spheroids prior the encapsulation. The dissolution procedure followed uses USP Apparatus 1 (basket) at 100 rpm in purified water at 37° C.

Conformance with the dissolution rate given in Table 1 provides the twenty-four hour therapeutic blood levels for the drug component of the extended release capsules of this invention in capsule form. Where a given batch of coated spheroids releases drug too slowly to comply with the desired dissolution rate study, a portion of uncoated spheroids or spheroids with a lower coating level may be added to the batch to provide, after thorough mixing, a loading dose for rapid increase of blood drug levels. A batch of coated spheroids that releases the drug too rapidly can receive additional film-coating to give the desired dissolution profile.

TABLE 1

Acceptable Coated Spheroid Dissolution Rates

Time (hours)	Average % Venlafaxine HCl released
2	<30
4	30–55
8	55–80
12	65–90
24	>80

Batches of the coated venlafaxine hydrochloride containing spheroids which have a dissolution rate corresponding to that of Table 1 are filled into pharmaceutically acceptable

capsules in an amount needed to provide the unit dosage level desired. The standard unit dosage immediate release (IR) tablet used presently provides amounts of venlafaxine hydrochloride equivalent to 25 mg, 37.5 mg, 50 mg, 75 mg and 100 mg venlafaxine. The capsules of this invention are filled to provide an amount of venlafaxine hydrochloride equivalent to that presently used in tablet form and also up to about 150 mg venlafaxine hydrochloride.

Dissolution of the venlafaxine hydrochloride ER capsules is determined as directed in the U. S. Pharmacopoeia (USP) using apparatus 1 at 100 rpm on 0.9 L of water. A filtered sample of the dissolution medium is taken at the times specified. The absorbance of the clear solution is determined from 240 to 450 nanometers (nm) against the dissolution medium. A baseline is drawn from 450 nm through 400 nm and extended to 240 nm. The absorbance at the wavelength of maximum absorbance (about 274 nm) is determined with respect to this baseline. Six hard gelatin capsules are filled with the theoretical amount of venlafaxine hydrochloride spheroids and measured for dissolution. Standard samples consist of venlafaxine hydrochloride standard solutions plus a gelatin capsule correction solution.

The percentage of venlafaxine released is determined from the equation

$$\%\ \text{Venlafaxine hydrochloride released} = \frac{(As)(Wr)(S)(V1)(0.888)(100)}{(Ar)(V2)(C)}$$

where As is absorbance of sample preparation, Wr is weight of reference standard, mg; S is strength of the reference standard, decimal; V1 is the volume of dissolution medium used to dissolve the dosage form, mL; 0.884 is the percent free base, Ar is the absorbance of the standard preparation, V2 is the volume of reference standard solution, mL; and C is the capsule claim in mg.

Table 2 shows the plasma level of venlafaxine versus time for one 75 mg conventional Immediate Release (IR) tablet administered every 12 hours, two 75 mg extended release (ER) capsules administered simultaneously every 24 hours, and one 150 mg extended release (ER) capsule administered once every 24 hours in human male subjects. The subjects were already receiving venlafaxine hydrochloride according to the dosage protocol, thus the plasma blood level at zero time when dosages were administered is not zero.

TABLE 2

Plasma venlafaxine level (ng/mL) versus time, conventional tablet (not extended release) versus ER capsule

Time (hours)	75 mg (IR)tablet (q 12 h)	2 × 75 mg (ER)capsules (q 24 hr)	1 × 150 mg (ER)capsules (q 24 h)
0	62.3	55.0	55.8
0.5	76.3		
1	135.6	53.3	53.2
2	212.1	69.8	70.9
4	162.0	138.6	133.3
6	114.6	149.0	143.5
8	86.7	129.3	129.5
10		118.4	114.4
12	51.9	105.1	105.8
12.5	74.7		
13	127.5		
14	161.3	90.5	91.3
16	134.6	78.2	78.5
18	106.2		

TABLE 2-continued

Plasma venlafaxine level (ng/mL) versus time, conventional tablet (not extended release) versus ER capsule

Time (hours)	75 mg (IR)tablet (q 12 h)	2 × 75 mg (ER)capsules (q 24 hr)	1 × 150 mg (ER)capsules (q 24 h)
20	83.6	62.7	63.3
24	57.6	56.0	57.3

Table 2 shows that the plasma levels of two 75 mg/capsule venlafaxine hydrochloride ER capsules and one 150 mg/capsule venlafaxine hydrochloride ER capsule provide very similar blood levels. The data also show that the plasma level after 24 hours for either extended release regimen is very similar to that provided by two immediate release 75 mg tablets of venlafaxine hydrochloride administered at 12 hours intervals.

Further, the plasma levels of venlafaxine obtained with the extended release formulation do not increase to the peak levels obtained with the conventional immediate release tablets given 12 hours apart. The peak level of venlafaxine from (ER), somewhat below 150 ng/ml, is reached in about six hours, plus or minus two hours, based upon this specific dose when administered to patients presently under treatment with venlafaxine hydrochloride (IR). The peak plasma level of venlafaxine, somewhat over 200 ng/ml, following administration of (IR) is reached in two hours and falls rapidly thereafter.

Table 3 shows venlafaxine blood plasma levels in male human subjects having a zero initial blood plasma level. Again, a peak blood plasma concentration of venlafaxine is seen at about 6 hours after dosing with venlafaxine hydrochloride extended release capsules in the quantities indicated. The subjects receiving the single 50 mg immediate release tablet showed a peak plasma level occurring at about 4. hours. For comparative purposes, the plasma levels of venlafaxine for subjects receiving the conventional formulated tablet can be multiplied by a factor of three to approximate the plasma levels expected for a single dose of 150 mg. conventional formulation.

TABLE 3

Plasma Blood Levels in Human Males Having No Prior Venlafaxine Blood Level

Time (Hours)	1 × 50 mg IR tablet	2 × 75 mg ER capsules	1 × 150 mg ER capsule
0	0	0	0
1	27.87	1.3	0
1.5	44.12	6.0	2.2
2	54.83	20.6	12.8
4	66.38	77.0	81.0
6	49.36	96.5	94.4
8	30.06	93.3	86.9
10	21.84	73.2	72.8
12	15.91	61.3	61.4
14	13.73	52.9	51.9
16	10.67	47.5	41.1
20	5.52	35.2	34.0
24	3.56	29.3	28.5
28	2.53	23.4	22.9
36	1.44	11.9	13.5
48	0.66	5.8	5.2

The blood plasma levels of venlafaxine were measured according to the following procedure. Blood samples from the subjects were collected in heparinized evacuated blood tubes and the tubes were inverted gently several times. As

quickly as possible, the tubes were centrifuged at 2500 rpm for 15 minutes. The plasma was pipetted into plastic tubes and stored at -20° C. until analysis could be completed.

To 1 mL of each plasma sample in a plastic tube was added 150 μL of a stock internal standard solution (150 μg/ml). Saturated sodium borate (0.2 mL) solution was added to each tube and vortexed. Five mL of ethyl ether was added to each tube which were then capped and shaken for 10 minutes at high speed. The tubes were centrifuged at 3000 rpm for 5 minutes. The aqueous layer was frozen in dry ice and the organic layer transferred to a clean screw cap tube. A 0.3 mL portion of 0.01 N HCl solution was added to each tube and shaken for 10 minutes at high speed. The aqueous layer was frozen and the organic layer removed and discarded. A 50 μL portion of the mobile phase (23:77 acetonitrile:0.1M monobasic ammonium phosphate buffer, pH 4.4) was added to each tube, vortexed, and 50 μL samples were injected on a Supelco Supelcoil LC-8-DB, 5 cm×4.6 mm, 5 μ; column in a high pressure liquid chromatography apparatus equipped with a Waters Lambda Max 481 detector or equivalent at 229 nm. Solutions of venlafaxine hydrochloride at various concentrations were used as standards.

EXAMPLE NO. 5

Manufactured by the techniques described herein, another preferred formulation of this invention comprises spheroids of from about 30% to about 35% venlafaxine hydrochloride and from about 0.3% to about 0.6% hydroxypropylmethylcellulose. These spheroids are then coated with a film coating, as described above, to a coating level of from about 5% to about 9%, preferably from about 6% to about 8%. A specific formulation of this type comprises spheroids of about 33% venlafaxine hydrochloride and about 0.5% hydroxypropylmethylcellulose, with a film coating of about 7%.

Lower dosage compositions or formulations of this invention may also be produced by the techniques described herein. These lower dosage forms may be administered alone for initial titration or initiation of treatment, prior to a dosage increase. They may also be used for an overall low-dose administration regimen or in combination with higher dosage compositions, such as capsule formulations, to optimize individual dosage regimens.

These lower dose compositions may be used to create encapsulated formulations, such as those containing doses of venlafaxine hydrochloride from about 5 mg to about 50 mg per capsule. Particular final encapsulated dosage forms may include, but are not limited to, individual doses of 7.5 mg, 12.5 mg, 18.75 mg, or 28.125 mg of venlafaxine HCl per capsule.

The spheroids useful in these lower dose formulations may comprise from about 5% to about 29.99% venlafaxine HCl, preferably from about 5% to about 25%, from about 75% to about 95% microcrystalline cellulose, and, optionally from about 0.25% to about 1.0% hydroxypropylmethylcellulose. The spheroids may be coated as described above, preferably with a film coating of from about 5% to about 10% by is weight. In some preferred formulations, the spheroids comprise the cited venlafaxine HCl and microcrystalline cellulose, with no hydroxypropylmethyl cellulose.

EXAMPLE NO. 6

Spheroids comprising 16.5% venlafaxine HCl and 83.5% microcrystalline cellulose were mixed with approximately 50% water (w/w) to granulate in a Littleford Blender Model FM-50E/1Z (Littleford Day Inc., P.O. Box 128, Florence, Ky. 41022-0218, U.S.A.) at a fixed speed of 180 rpm. The blended material was extruded through a 1.25 mm screen using a Nica extruder/speronization machine (Aeromatic-Fielder Division, Niro Inc., 9165 Rumsey Rd., Columbia, Md. 21045, U.S.A.) for a 12/20 mesh cut after drying. Two portions of the resulting spheroids were coated with a 5% and 7% coating level, respectively, by techniques described above using the coating formulation:

Ingredient	% (w/w)
Methylene Chloride	60.000
Methanol Anhydrous	35.500
Ethylcellulose, NF, HG 2834, 50 cps	3.825
Hydroxypropyl Methylcellulose, 2910 USP, 6 cps	0.675

These 5% and 7% coated lots were tested for dissolution on a Hewlett Packard automated dissolution system over a 24 hour period, resulting in the following dissolution patterns

Time/hr	% Dissoluded 16.5%/5%	% Dissolved 16.5%/7%
2	12.4	5.6
4	42.8	25.4
8	70.7	60.4
12	82.2	75.4
24	94.3	92.7

EXAMPLE NO. 7

A formulation of spheroids containing 8.25% venlafaxine HCl and 91.75% microcellulose was prepared according to the techniques of Example No. 6 and coated with a 5% film coating. In the Hewlett Packard automated dissolution system these spheroids provided the following dissolution profile:

Time/hr	% Dissolved 8.25%/5%
2	4.4
4	24.2
8	62.9
12	77.8
24	93.5

Thus, the desired dissolution rates of sustained release dosage forms of venlafaxine hydrochloride, impossible to achieve with hydrogel tablet technology, has been achieved with the film-coated spheroid compositions of this invention.

What is claimed is:

1. An extended release formulation of venlafaxine hydrochloride comprising a pharmaceutically acceptable capsule containing spheroids comprised of from about 6% to about 40% venlafaxine hydrochloride by weight, about 50% to about 94% microcrystalline cellulose, NF, by weight, and optionally from about 0.25% to about 1% by weight of hydroxypropyl-methylcellulose, USP, wherein the spheroids are coated with a film coating composition comprised of ethyl cellulose and hydroxypropylmethylcellulose.

2. An extended release formulation of venlafaxine hydrochloride according to claim 1 which provides peak serum levels of up to 150 ng/ml and extended therapeutically effective plasma levels over a twenty four hour period.

3. An extended release formulation according to claim 1 wherein the spheroids are coated with from about 2% to about 12% of total formulation weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

4. An extended release formulation according to claim 1 wherein the spheroids are comprised of from about 30% to 40% venlafaxine hydrochloride by weight, about 50% to about 70% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP.

5. An extended release formulation according to claim 4 wherein the spheroids are coated with from about 2% to about 12% of total formulation weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

6. An extended release formulation according to claim 1 wherein the spheroids comprise from about 6% to about 30% venlafaxine hydrochloride by weight, about 70.1% to about 94% microcrystalline cellulose, NF, by weight and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

7. An extended release formulation according to claim 6 wherein the spheroids are coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

8. An extended release formulation according to claim 1 wherein the spheroids comprise from about 5% to about 25% venlafaxine hydrochloride and from about 95% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

9. An extended release formulation according to claim 6 wherein the spheroids comprise from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

10. An extended release formulation according to claim 6 wherein the spheroids comprise from about 6% to about 20% venlafaxine hydrochloride and from about 94% to about 80% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

11. An encapsulated, extended release formulation of venlafaxine hydrochloride according to claim 1 having the following dissolution profile in USP Apparatus 1 (basket) at 100 rpm in purified water at 37° C:

Time (hours)	Average % Venlafaxine HCl released
2	<30
4	30–55
8	55–80
12	65–90
24	>80

12. An extended release formulation according to claim 1 wherein the spheroids are composed of about 37% by weight of venlafaxine hydrochloride, about 0.5% by weight of hydroxypropylmethylcellulose, and about 62% by weight of microcrystalline cellulose.

13. An extended release formulation according to claim 1 wherein the film coating is comprised of ethyl cellulose (4.81% of total weight) and hydroxypropylmethylcellulose (0.85% of total weight).

14. An extended release formulation according to claim 1 wherein the film coating comprises 6–8% by weight of total weight.

15. An extended release formulation according to claim 1 wherein the film coating is comprised of ethyl cellulose (2.48% of total weight) and hydroxypropylmethylcellulose (0.437% of total weight).

16. An extended release formulation according to claim 1 wherein the film coating composition is comprised of ethyl cellulose having a 44.0–51.0% content of ethoxy groups and hydroxypropylmethylcellulose having a methoxy content of 28.0–30.0% and a hydroxypropoxy group content of 7.0–12.0%.

17. An extended release formulation according to claim 1 wherein the film coating composition is comprised of about 85% by total weight of film coating of ethyl cellulose having 44.0–51% content of ethoxy groups and about 15% by total weight of film coating of hydroxypropylmethylcellulose having a methoxy content of 28.0–30.0% and a hydroxypropoxy group content of 7.0–12.0%.

18. An extended release formulation according to claim 1 wherein the film coating composition is comprised of 85% by weight of ethyl cellulose having an ethoxy content of 44.0–51% and a viscosity of 50% cps for a 5% aqueous solution, and 15% by weight of hydroxypropylmethylcellulose having a viscosity of 6 cps at 2% aqueous solution with a methoxy content of 28–30% and a hydroxypropoxy content of 7–12%.

19. An extended release formulation of venlafaxine hydrochloride for once daily administration which comprises spheroids containing 37.3% venlafaxine, 62.17% microcrystalline cellulose and 0.5% hydroxypropylmethylcellulose coated with a quantity of a mixture comprised of 85% ethyl cellulose and 15% hydroxypropylmethylcellulose sufficient to give coated spheroids having a dissolution profile in USP Apparatus 1 (basket) at 100 rpm in purified water at 37° C.:

Time	Average % Venlafaxine HCl Released
2	<30
4	30–55
8	55–80
12	65–90
24	>80.

20. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty four hour period with diminished incidences of nausea and emesis which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides

a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

21. A method for eliminating the troughs and peaks of drug concentration in a patients blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

22. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty-four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof, an encapsulated extended release formulation that provides a peak blood plasma level of venlafaxine in from about 5 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

23. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty-four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof, an encapsulated extended release formulation that provides a peak blood plasma level of venlafaxine in about 6 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

24. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about 5 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

25. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in about 6 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

* * * * *

EXHIBITS 12 – 15
REDACTED

Exhibit 16

United States Patent [19]

McAinsh et al.

[11] **4,138,475**

[45] **Feb. 6, 1979**

[54] **SUSTAINED RELEASE PHARMACEUTICAL COMPOSITION**

[75] Inventors: **James McAinsh; Raymond C. Rowe,** both of Macclesfield, England

[73] Assignee: **Imperial Chemical Industries Limited,** London, England

[21] Appl. No.: **833,339**

[22] Filed: **Sep. 14, 1977**

[30] **Foreign Application Priority Data**

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[52] **U.S. Cl.** **424/19;** 424/20; 424/21

[58] **Field of Search** 424/19–22, 424/35, 362

[56] **References Cited**

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Primary Examiner—Shep K. Rose

Attorney, Agent, or Firm—Cushman, Darby & Cushman

[57] **ABSTRACT**

Sustained release pharmaceutical composition consisting of a hard gelatine capsule containing film coated spheroids, the spheroids comprising propranolol, or a pharmaceutically-acceptable salt thereof, in admixture with non-water-swellable microcrystalline cellulose, and the said spheroids having a film coat comprising ethylcellulose optionally together with hydroxypropyl methylcellulose and/or a plasticizer.

9 Claims, No Drawings

SUSTAINED RELEASE PHARMACEUTICAL COMPOSITION

This invention relates to a sustained release pharmaceutical composition and more particularly it relates to a sustained release pharmaceutical composition containing propranolol or a pharmaceutically-acceptable acid-addition salt thereof.

Propranolol hydrochloride is an important medicament which is widely used throughout the world. It is a β-adrenergic blocking agent which is mainly used for the treatment of angina pectoris, cardiac arrhythmias and hypertension. The chemical name for propranolol is dl-1-isopropylamino-3-(1-naphthoxy)-2-propanol. This compound and its acid-addition salts, and processes of manufacture thereof, are claimed in our United Kingdom patent No. 994,918. Furthermore, pharmaceutical compositions comprising at least one of these substances in admixture with a pharmaceutically-acceptable diluent or carrier are claimed in our United Kingdom patent No. 995,800. The present invention relates to a new sustained release pharmaceutical composition which is not disclosed in, nor rendered obvious by, said patent No. 995,800 nor elsewhere in the art.

According to the invention there is provided a sustained release pharmaceutical composition consisting of a hard gelatine capsule containing film coated spheroids, the said spheroids comprising, prior to coating, 40 to 65% by weight of propranolol or a pharmaceutically-acceptable acid-addition salt thereof in admixture with non-water-swellable microcrystalline cellulose, and the said spheroids having a film coat comprising ethylcellulose optionally together with hydroxypropyl methylcellulose.

The term "spheroid" is well known in the pharmaceutical art, and means a spherical granule having a diameter of approximately 0.5 to 2mm. As a particularly suitable salt of propranolol there may be mentioned, for example, the hydrochloride. A suitable microcrystalline cellulose is, for example, the material sold as Avicel-PH-101 (available from FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook, Pa, U.S.A.). According to one embodiment of the invention the uncoated spheroids may, for example, contain 50 to 60% by weight of propranolol hydrochloride and 50 to 40% by weight of microcrystalline cellulose, respectively.

A suitable form of ethylcellulose is that having a viscosity in the range of 5 to 100 cps at 20° C. (U.S. National Formulary XIII) (content of ethoxy groups 44 to 51% by weight), and more particularly a viscosity of 50 cps at 20° C. (content of ethoxy groups 48 to 49% by weight). A suitable form of hydroxypropyl methylcellulose is that having a viscosity in the range 3 to 100 cps at 20° C. (U.S. National Formulary XIII), and more particularly a viscosity of 6 cps at 20° C. The film coat may, for example, comprise 80 to 100% by weight of ethylcellulose and 20 to 0% by weight of hydroxypropyl methylcellulose, and more particularly 90% by weight of ethylcellulose and 10% by weight of hydroxypropyl methylcellulose. In addition, the film coat may optionally contain up to 20% by weight of a plasticizer, for example a vegetable oil, for example castor oil, or glycerol, or a glyceryl ester of a fatty acid, for example glyceryl triacetate or glyceryl monoricinoleate. The film coat may comprise 5 to 15% by weight of the coated spheroids, and preferably 9 to 10% by weight thereof.

The sustained release composition of this invention may, for example, contain 100 to 200mg., and more particularly 160mg., of the medicament, for example propranolol hydrochloride.

The sustained release compositions of this invention may be manufactured by well known pharmaceutical manufacturing methods. For example, the spheroids may be manufactured on a conventional spheroniser in which a horizontal, rough-surfaced plate rotates inside a stationary vertical cylinder, and then film coated in conventional manner in a perforated coating drum, and finally the film coated spheroids filled into hard gelatine capsules using a conventional encapsulation machine.

The invention is illustrated but not limited by the following Example.

EXAMPLE

Propranolol hydrochloride (60kg.) and microcrystalline cellulose (Avicel-PH-101; 40kg.) were blended together in a 450 litre planetary mixer. Water (50kg.) was added, and the mixer was run for 10 minutes until a homogeneous, plastic mass was obtained. The mass was extruded under pressure through a perforated cylinder to give cylindrical extrudates of nominally 1mm. diameter.

The damp extrudates (in batches of 15 to 20kg.) were placed in a spheroniser in which the rotating disc (diameter 68cm.) rotated at 300 to 400 r.p.m. The rotation was continued for 10 minutes, and the resulting spheroids were then dried at 60° C. in a fluidised bed drier. The dried spheroids were passed over a 1.4mm. screen, and those which passed through were subjected to a 0.7mm. screen. The over-and under-sized spheroids were discarded.

Acceptable spheroids (100kg.) were placed in a perforated coating drum fitted with a 0.5mm. screen and rotating at 17 r.p.m. A film formulation consisting of ethylcellulose (9kg.) and hydroxypropyl methylcellulose (1kg.) dissolved in a mixture of dichloromethane (100 liter) and methanol (100 liter) was sprayed onto the rotating spheroids at a rate of 750ml. per minute using a standard airless spray system. The resulting film coated spheroids were passed over a 1.4mm. screen to remove any aggregates, and then filled into hard gelatine capsules using a conventional encapsulation machine, such that each capsule contained 160mg. of propranolol hydrochloride. There was thus obtained a sustained release composition containing propranolol hydrochloride.

What we claim is:

1. A sustained release pharmaceutical composition consisting of a hard gelatine capsule containing film coated spheroids, the said spheroids comprising, prior to coating, 40 to 65% by weight of propranolol, or a pharmaceutically-acceptable acid-addition salt thereof, in admixture with non-water-swellable microcrystalline cellulose, and the said spheroids having a film coat comprising ethylcellulose or ethycellulose and hydroxpropyl methylcellulose.

2. The composition claimed in claim 1 in which the uncoated spheroids contain 50 to 60% by weight of propranolol hydrochloride and 50 to 40% by weight of non-water-swellable microcrystalline cellulose, respectively.

3. The composition claimed in claim 1 in which the film coat comprises 5 to 15% by weight of the coated spheroids.

4. The composition claimed in claim 1 in which the ethylcellulose has a viscosity of 50 cps at 20° C.

5. The composition claimed in claim 1 in which the hydroxypropyl methylcellulose has a viscosity of 6 cps at 20° C.

6. The composition claimed in claim 1 in which the film coat comprises 80 to 100% by weight of ethylcellulose and 20 to 0% by weight of hydroxypropyl methylcellulose.

7. The composition claimed in claim 1 in which the film coat contains up to 20% by weight of a plasticizer.

8. The composition claimed in claim 1 which contains 100 to 200 mg. of propranolol or a pharmaceutically-acceptable acid-addition salt thereof.

9. The composition claimed in claim 1 in which, prior to coating, the spheroids contain 60% by weight of propranolol hydrochloride in admixture with 40% by weight of non-water-swellable microcrystalline cellulose, and the spheroids have a film coat consisting of 90% by weight of ethylcellulose having a viscosity of 50 cps at 20° C. and 10% by weight of hydroxypropyl methylcellulose having a viscosity of 6 cps at 20° C., the film coat comprising 9 to 10% by weight of the coated spheroids, and the said composition containing 160 mg. of propranolol hydrochloride.

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EXHIBITS 17 – 21
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Exhibit 22

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(54) Title: ANTIDEPRESSANT DOSAGE FORM

(57) Abstract

The invention pertains to a dosage form (10) and to administering an antidepressant medicament (16) for an extended period of time in a rate-known dose.

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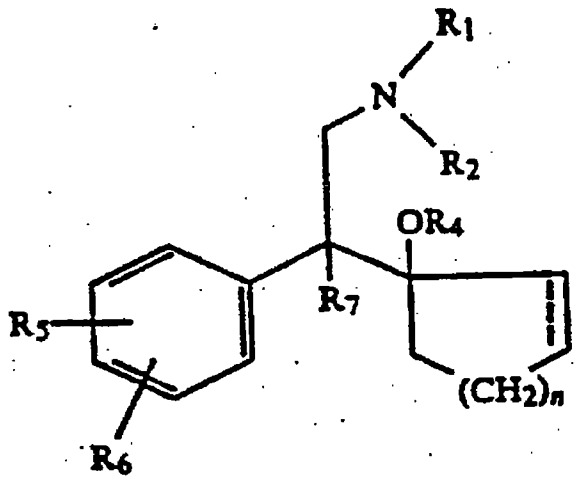
ANTIDEPRESSANT DOSAGE FORM

FIELD OF THE INVENTION

This invention pertains to a controlled-release dosage form comprising a compound of the following structural formula:



useful for antidepressant therapy. The invention concerns also a method useful for antidepressant therapy by administering the controlled-release dosage form comprising the compound of the formula.

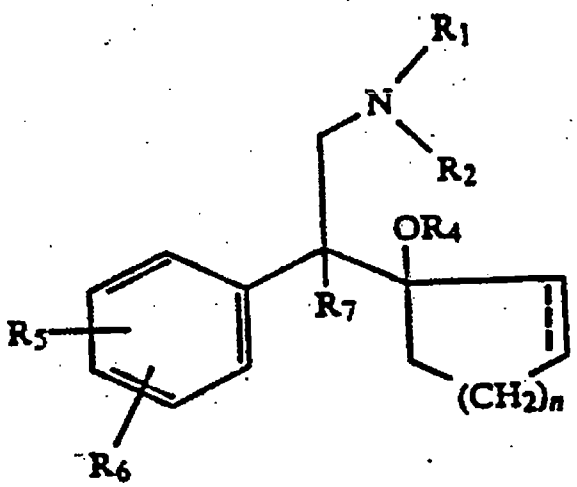
BACKGROUND OF THE INVENTION

The primary goal of drug administration is to provide a therapeutic dose of drug in the body to achieve a desired blood concentration, and then maintain the desired drug blood concentration. The prior art, in attempts to obtain the desired therapeutic effect, often used different dosage forms or programs. One dosage program consists of a single dosing of the drug from a conventional capsule or tablet that produced a

rapid rise followed by an immediate decline of the drug blood level versus time. The single dosing does not maintain the drug within a therapeutic range for an extended period of time, but exhibits of a short duration of action due to the inability of the conventional dosage form to provide drug delivery over time.

Another prior art dosing program used to obtain and to achieve drug blood levels consists in administering the drug repetitively using conventional dosage forms at various dosing intervals, as in multiple-dose therapy. In administering a drug according to the multiple-dose therapy, the drug blood level reached and the time required to reach that level depends on the dose and the dosing interval. There are, however, several potential problems inherent in multiple dose therapy. For example, if the dosing interval is not appropriate for the biological half-life of the drug, large peaks and valleys may result in the drug blood levels. Also, the drug blood level may not be within the therapeutic range at sufficiently early times, an important consideration for many disease states. And too, patient noncompliance with the multiple dosing regimen can result in a failure of this approach, especially as a drug in circulation surges to a high each time the drug is administered followed by a decline in drug concentration in the blood and in body compartments. Thus, a graph of drug in circulation following a dosage program of several doses, has an appearance of a series of peaks, which may surpass the toxic threshold. Then, each time the blood levels decreases into valleys, below a critical level needed to achieve a desired therapeutic effect, that effect may not be obtainable in the blood and body. Conventional dosage forms and their mode of operation are discussed in Remington's Pharmaceutical Sciences, 18th Edition, pages 1676 to 1686, (1990), Mack Publishing Co.; The Pharmacological Basis of Therapeutics, 7th Edition, page 7 (1985) published by MacMillian Publishing Co., and in United States Pat. Nos. 3,598,122 and 3,598,123 both issued to Zaffaroni.

A critical need exists for a controlled-rate dosage form for administering the drug of the formula:



which drug is presently administered in conventional dosage forms including tablets, capsules, elixirs and suspensions. These conventional dosage forms produce the peaks and valleys drug pattern presented above and they do not provide for controlled-rate therapy over an extended period of time. The drug of the formula is dosed twice or thrice a day now because of its elimination half-life of three to five hours. This pattern of dosing indicates the need for a controlled-release dosage form that can administer the drug at a controlled rate over an extended time to provide constant therapy and thereby eliminate the need for multiple

dosing. The drugs of the structural formula are known in United States Patent Nos. 4,535,186; 4,611,078; and 4,761,501 all issued to Husbands, Yardley and Muth.

The prior art provided controlled-release dosage forms that can continuously over time administer a drug for controlled-rate therapy. For example, in United States Pat. No. 4,327,725 issued to Cortese and Theeuwes and in United States Pat. Nos. 4,612,008; 4,765,989; and 4,783,337 issued to Wong, Barclay, Deters, and Theeuwes. The dosage forms disclosed in these patents provide a drug at a constant rate for effecting a therapeutic range for preferred therapy. The dosage forms of the patents provide a therapeutic range and avoids delivering the drug in excess in a toxic range with its accompanying side-effects. The dosage forms of the patents in providing a controlled dose in a therapeutic range also avoids delivering the drug in an ineffective dose in an ineffective range.

The dosage forms presented immediately above operate successfully for their intended use and they can deliver many drugs indicated for good therapy. The drugs of the above structural formula, however, possess properties such as a high solubility of 570 mg per ml at a body temperature of 37°C. that can lead to a premature release of the drug from the dosage form. During operation of the dosage forms, the convection motion of the imbibed fluid, and the hydrostatic pressure of the imbibed fluid coupled with the high solubility can result in the premature release of the drugs of the formula.

It is immediately apparent in the light of the above presentation that an urgent need exists for a dosage form endowed with controlled-release delivery for delivering the drugs embraced by the structural formula. The need exists for the dosage form for delivering the drug at a

controlled dose in a therapeutic range while simultaneously providing the intended therapy. It will be appreciated by those versed in the dispensing art, that such a dosage form that can administer the drug in a controlled-rate dose over time, would, represent an advancement and a valuable contribution to the art.

OBJECTS OF THE INVENTION

Accordingly, in view of the above presentation, it is an immediate object of this invention to provide a dosage from that possesses controlled-release delivery for providing a dosage form for administering a drug of the structural formula.

Another object of the present invention is to provide a dosage form for administering the drug of the formula in a controlled-rate dose in a therapeutic range over a prolonged period of time.

Another object of the present invention is to provide a dosage form that can deliver the drug of the formula essentially-free of a premature release from the dosage form.

Another object of the present invention is to provide a drug delivery controlled-release system that can deliver a drug for maintaining constant drug levels in the blood thereby functioning as a prolonged release system.

Another object of the present invention is to provide drug delivery sustained-release system that provides slow release of the drug over an extended period of time optionally in a therapeutic range.

Another object of the present invention is to provide a dosage form that substantially reduces and/or substantially eliminates the unwanted influences of a gastrointestinal environment of use and still provides controlled drug administration.

Another object of the present invention is to provide an improvement in a dosage form for administering a drug embraced by the structural formula and its pharmaceutically acceptable salt, wherein the improvement comprises delivering the drug in a controlled-release rate from the dosage form for improved and known therapy.

Another object of the invention is to provide a once-a-day controlled-release dosage form to deliver the drug of the structural formula orally to a patent in need of therapy.

Another object of the invention is to provide a method for administering a drug of the formula by orally administering the drug in a controlled rate dose per unit dose over an extended time to an animal in need of therapy.

Another object of the present invention is to provide a method for administering a drug of the formula in a therapeutic range while simultaneously substantially-avoiding a toxic range and an infective range.

Another object of the present invention is to provide a therapeutic composition comprising a drug of the structural formula blended with a drug-composition forming polymer.

Another object of the invention is to provide a therapeutic composition comprising a member selected from the group consisting of

venlafaxine and its pharmaceutically acceptable additional salt and a pharmaceutically acceptable polymer carrier for venlafaxine and its acceptable salts.

Other objects, feature, and advantages of the invention will more apparent to those versed in the dispensing arts from the following detailed specification, taken in conjunction with the drawings and the accompanying claims.

BRIEF DESCRIPTION OF THE DRAWINGS

In the drawing figures, which are not drawn to scale, but are set forth to illustrate various embodiments of the invention, the drawing figures are as follows:

Drawing Figure 1 is a general view of a dosage form provided by the invention, which dosage form is designed and shaped for oral administration, and for a drug delivery in a controlled-rate dose in the gastrointestinal tract;

Drawing Figure 2 is an opened view of the dosage form of drawing Figure 1 for depicting the structure of the dosage form and the composition member contained inside the dosage form; and

Drawing Figure 3 is a view of a dosage form that depicts an external, instant-release of drug of the structural formula coated on the exterior surface of the dosage form.

In the drawing figures, and in the specification, like parts in related figures are identified by like numbers. The terms appearing earlier in the

specification and in the description of the drawing figures, as well as embodiments thereof, are further described elsewhere in the disclosure.

DETAILED DESCRIPTION OF THE DRAWINGS

Turning now to the drawing figures in detail, which drawing figures are examples of dosage forms provided by this invention, and which examples are not to be construed as limiting, one example of a dosage form is seen in drawing Figure 1. In drawing Figure 1, a dosage form 10 is seen comprising a body member 11, which body 11 comprises wall 12, that surrounds and forms an internal area, not seen in drawing Figure 1. Dosage form 10 comprises at least one exit port 13 for connecting the exterior with the interior of dosage form 10.

The dosage form 10 of drawing Figure 1 illustrates a controlled-release dosage form manufactured as an osmotic dosage form that delivers a drug by osmotic action over an extended period of time. The dosage form comprising controlled-release properties embraced by this invention are successful at maintaining substantially constant drug levels in the blood or in a tissue. The dosage forms within the mode and manner of this invention comprises also sustained-release dosage forms. The sustained-release dosage forms releases the drug and provide drug levels in the blood or target tissue within a therapeutic range over an extended period of time. The invention embraces additionally prolonged release dosage forms. The prolonged release dosage form denotes extended duration of drug delivery action over that achieved by conventional drug delivery.

In drawing Figure 2, dosage form 10 of Figure 1 is seen in opened section. In drawing Figure 2, dosage form 10 comprises a body 11, a wall 12 that surrounds and defines an internal compartment 14. In

drawing Figure 2, internal compartment 14 communicates through an exit passageway 13 with the exterior of dosage form 10.

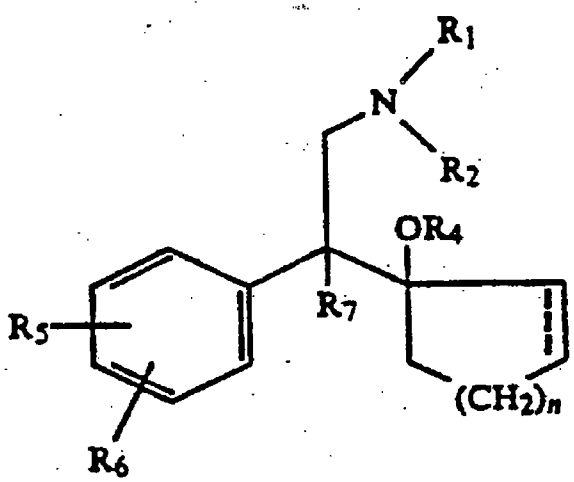
Wall 12 of dosage form 10 comprises totally or in at least a part of a composition that is permeable to the passage of an exterior fluid present in an environment of use, such as aqueous and biological fluids. Wall 12 is formed of nontoxic ingredients, is substantially impermeable to the passage of a drug and other ingredients present in compartment 14. Wall 12 comprises a composition that is substantially inert, that is, wall 12 maintains its physical and chemical integrity during the drug dispensing life of a drug from dosage form 10. The phrase, "maintaining its physical and chemical integrity," means wall 12 does not lose its structure and it does not change during the dispensing life of dosage form 10, except for possible leaching of one or more exit 13 passageway formed during operation of dosage form 10 or for leaching a water-soluble flux enhancers blended into wall 12. Wall 12 comprises a material that does not adversely affect an animal, a human or any other components comprising the dosage form. Representative materials for forming wall 12, are in one embodiment, a cellulose ester polymer, a cellulose ether polymer and a cellulose esterether polymer. These cellulosic polymers have a degree of substitution. D.S., on the anhydroglucose unit, from greater than 0 up to 3 inclusive. By degree of substitution is meant the average number of hydroxyl groups originally present on the anhydroglucose unit comprising the cellulose polymer that are replaced by a substituting group. Representative materials include a member selected from the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, mono-, di- and tricellulose alkanylates, mono-,di-, and tricellulose aroylates, and the like. Exemplary polymers include cellulose acetate having a D.S. up to 1 and an acetyl content up to 21%; cellulose acetate having a D.S. of 1 to 2 and an acetyl content of 21 to 35 %;

cellulose acetate having a D.S. of 2 to 3 and an acetyl content of 35 to 44.8%, and the like. More specific cellulosic polymers include cellulose propionate having a D.S. of 1.8 and a propyl content of 39.2 to 45% and a hydroxyl content of 2.8 to 5.4%; cellulose acetate butyrate having a D.S. of 1.8, an acetyl content of 13 to 15% and a butyryl content of 34 to 39%; cellulose acetate butyrate having an acetyl content of 2 to 29%, a butyryl content of 17 to 53% and a hydroxyl content of 0.5 to 4.7; cellulose triacylates having a D.S. of 2.9 to 3 such as cellulose trivalerate, cellulose trilaurate, cellulose tripalmitate, cellulose trisuccinate, and cellulose trioctanoate; cellulose diacylates having a D.S. of 2.2 to 2.6 such as cellulose disuccinate, cellulose dipalmitate, cellulose dioctanoate, cellulose dipentanoate, co-esters of cellulose such as cellulose acetate butyrate and cellulose acetate propionate, and the like.

Additional polymers include ethyl cellulose of various degree of etherification with ethoxy content of from 40% to 55%, acetaldehyde dimethyl cellulose acetate, cellulose acetate ethyl carbamate, cellulose acetate methyl carbamate, cellulose acetate diethyl aminoacetate, semipermeable polyamides; semipermeable polyurethanes; semipermeable sulfonated polystyrenes; semipermeable cross-linked selective polymers formed by the coprecipitation of a polyanion and a polycation as disclosed in U.S. Pat Nos. 3,173,876, 3,276,586, 3,541,005; 3,541,006, and 3,546,142; semipermeable polymers as disclosed by Loeb and Sourirajan in U.S. Pat. No. 3,133,132; semipermeable lightly cross-linked polystyrene derivatives, semipermeable cross-linked poly(sodium styrene sulfonate); semipermeable cross-linked poly(vinylbenzyltrimethyl ammonium chloride); semipermeable polymers exhibiting a fluid permeability of 2.5×10^{-8} to 2.5×10^{-4} (cm^2/hr.atm) expressed per atmosphere of hydrostatic or osmotic pressure difference across the semipermeable wall. The polymers are known to the art in U.S. Pat. Nos. 3,845,770; 3,916,899; and 4,160,020; and in Handbook

of Common Polymers by Scott, J. R. and Roff, W. J., 1971 published by CRC Press, Cleveland, OH.

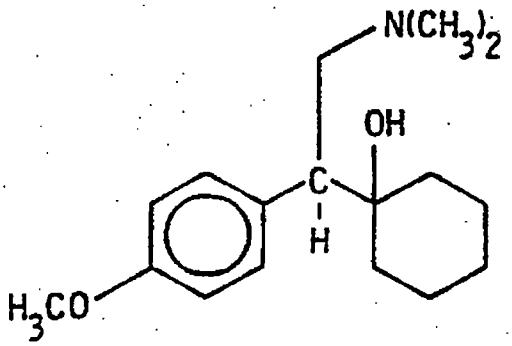
Compartment 14 comprises a drug composition, identified as drug layer 15 which contains drug 16, identified by dots. Drug 16 comprises a drug of the following structural formula:



wherein the dotted line represents optional unsaturation or a cycloalkenyl moiety; R_1 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbon atoms; R_2 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbon atoms; R_4 is a member selected from the group consisting of hydrogen, alkyl of 1 to 6 carbon atoms, formyl, and alkanoyl of 2 to 7 carbon atoms; R_5 and R_6 are independently a member selected from the group consisting of hydrogen, hydroxyl, an alkyl of 1 to 6 carbon atoms, an alkoxy of 1 to 6 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, nitro, alkylmercapto of 1 to 6 carbon atoms, amino, alkylamino of 1 to 6 carbon atoms in which each alkyl group comprises 1 to 6 carbon atoms, alkanamido of 2 to 7 carbon

atoms, halo, and trifluoroethyl, R_7 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbons, and n is one of the integers 0, 1, 2, 3, and 4. The formula embraces also the pharmaceutically acceptable addition salts including a member selected from the group consisting of inorganic, organic, hydrochloric, hydrobromic, gluconic, fumaric, maleric, sulfonic, succinic, sulfuric, phosphoric, tartaric, acetic, proponic, citric, oxalic and similar pharmaceutically acceptable addition salts. The compounds are known in U.S. Pat. Nos. 4,535,186; 4,611,078; 4,761,501; and 5,190,765.

The drugs of the structural formula are represented by the drug 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol of the structural formula:



The drug embraced by the formula possesses antidepressant properties. The drug in vitro prevents the neuronal uptake of serotonin, morepinephrine, and dopamine and it does not inhibit monoamine oxidase. The drug antagonizes reserpine-induced hypothermia and potentiates the effects of levodopa, and reduces histamine-induced

corticotropin release and induces cyclicadenosine monophosphate subsensitivity after both acute and chronic administration. The drug possesses excellent antidepressant activity in humans. The therapeutic amount of drug 16 in dosage form 10 is 0.5 mg to 750 mg, with individual dosage forms comprising 2, 5, 10, 25, 40, 50, 75, 100, 150, 250, 300, 500, and 600 mg of drug 16 for administering in a single dose or in more then one dose over an extended period of 24 hours. The therapeutic properties of the drug embraced by the structural formula are reported in Current Therapeutic Research, Vol. 42, No. 5, pages 901 to 909 (1987).

Composition 15 comprising drug 16 may comprise a drug dispensing carrier and composition formulating member consisting of a member selected from the group consisting of 0 wt% to 25 wt% of a hydroxypropylalkylcellulose where alkyl consists of 1 to 7 carbons selected from the group consisting of methyl, ethyl, isopropyl, butyl, pentyl, and hexyl which cellulose member comprises a 9,000 to 1,250,000 molecular weight and is exemplified by hydroxypropylmethylcelluose, hydroxypropylethylcellulose, hydroxypropylisopropylcellulose, hydroxypropylbutylcellulose and hydroxypropylhexylcellulose represented by dashes 17; a member selected from the group consisting of 0 wt% to 20 wt% hydroxylalkylcellulose where alkyl is 1 to 6 carbons including methyl, ethyl, propyl, butyl, pentyl, and hexyl which cellulose member comprises a 7,500 to 750,000 molecular weight and is exemplified by hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxyisopropylcellulose and hydroxybutylcellulose as represented by slanted line 18; a member selected from the group consisting of 0 wt% to 35 wt% of a vinyl-polymer having a 3,500 to 750,000 molecular weight represented by poly-n-vinylamide, poly-n-vinlycetamide, poly-n-vinylethylacetamide, poly-n-vinylmethylpropionamide, poly-n-vinyl

ethylpropionamide, poly-n-vinylmethylisobutyramide, poly-n-vinyl-2-pyrrolidone, poly-n-vinypiperidone also known as polyvinylpyrrolidone and as poly-n-vinylpyrroledone, poly-n-vinylcaprolactam, poly-n-vinyl-5-methyl-2-pyrrolidone and poly-n-vinyl-3-methyl-2-pyrrolidone, and poly-n-vinylpyrrolidone copolymer with a member selected from the group consisting of vinyl acetate, vinyl alcohol, vinyl chloride, vinyl fluoride, vinyl butyrate, vinyl laurate and vinyl stearate represented by small circles 19; and 0 wt%, where wt% is weight percent, 35 wt% of a maltodextrin polymer composition comprising the formula $(C_6H_{12}O_5)_n H_2O$ wherein n is 3 to 7,500 and the maltodextrin polymer comprises a 500 to 1,250,000 number average molecular weight represented by a small square 20; as member selected from the group consisting of 0 wt% to 40 wt% of poly(etheylen oxide) having a molecular weight of 100,000 to 600,000 grams per mole, represented by half-circles 20a. Composition 15 optionally comprises from 0 to 4.5 wt% of a lubricant represented by magnesium stearate, calcium stearate or stearic acid. The total weight of all ingredients in composition 15 is equal to 100 wt%, weight percent.

Compartment 14 comprises a displacement composition or push layer 21. Displacement composition 21 comprises a polymer member selected from the group consisting of a polymer possessing a repeating molecular unit $-(-O-CH_2CH_2-)_n$ wherein n is a positive whole number of 50,000 to 300,000 as represented by a poly(alkylene oxide) comprising poly(ethylene oxide) seen as wavy line 22; a maltodextrin polymer of the formula $(C_6H_{12}O_5)_n H_2O$ wherein n is 50 to 62,000 and comprises a 9,000 to 10,000,000 molecular weight and represented by triangle 23; a carboxymethylcellulose polymer comprising a 10,000 to 5,000,000 molecular weight represented by alkali carboxymethylcellulose, sodium carboxymethylcellulose and potassium carboxymethylcellulose, ammonium carboxymethylcellulose, sodium carboxymethyl-2-hydroxyethylcellulose, sodium carboxymethyl-methylcellulose, alkali

carboxymethyl-hydroxypropyl-methylcellulose, alkali carboxymethyl-2-hydroxyethylmethylcellulose, alkali carboxymethyl-2-hydroxybutylmethylcellulose, alkali carboxymethyl-2-hydroxyethyl-ethylcellulose and alkali carboxymethyl-2-hydroxypropylcellulose, where alkali is sodium and potassium and seen in drawing Figure 2 as hexagonal 23a. The polymers in push layer 21 provide unforeseen operating advantages as the polymer maintains its chemical composition during operation as it imbibes an external aqueous fluid including biological fluid while simultaneously pushing the drug from the dosage form essentially-free of substantially mixing the drug composition with the push composition. The displacement composition 21 comprises optionally from 4 to 35 wt% of an osmotically active compound, also known as osmagent and represented by vertical line 24. Representative of osmotically effective compounds comprises salts, oxides, esters that exhibit imbibition properties, carbohydrates and acids including a member selected from the group consisting of magnesium sulfate, magnesium chloride, sodium chloride, lithium chloride, potassium chloride, potassium sulfate, sodium sulfate, sodium sulfite, lithium sulfate, ammonium chloride, potassium lactate, mannitol, urea, magnesium succinate, tartaric acid, raffinose, sorbitol, sucrose, fructose, and glucose. Displacement layer 21 optionally comprises 0.5 wt % to 30 wt% of a cellulose polymer 25 represented by the letter v. Representative of cellulose polymer 25 comprise a member selected from the group consisting of hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxypropylethylcellulose, hydroxypropylisopropylcellulose, hydroxypropylbutylcellulose, hydroxypropylpentylcellulose, and hydroxypropylhexylcellulose comprising a 9,000 to 225,000 molecular weight. The displacement composition optionally comprises 0 wt% to 5 wt% of lubricant stearic acid and, magnesium stearate, calcium oleate, oleic acid, and caprylic acid. The polymers are known in U.S. Pat Nos.

3,845,770; and 4,160,020; in Handbook of Common Polymers by Scott, J. R., and Roff, W. J., published by CRC Press, Cleveland, OH.

Dosage form 10, a seen in drawing Figure 3 depicts another preferred manufacture provided by the invention. Dosage form 10, in drawing Figure 3, comprises an external coat on a the exterior surface of dosage form 10. Coat 26 is a therapeutic composition comprising 10 mg to 150 mg of drug 16, represented by dots 16. Exterior coat 26 provides instant drug 16 for instant therapy. Drug 16 is blended with an aqueous-soluble composition comprising a carrier methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and blends of hydroxypropylcellulose and hydroxypropylmethylcellulose. Coat 26 optionally comprises polyethylene glycol or acetylated triglycerides. Coat 26 provides instant therapy as coat 26 dissolves or undergoes dissolution in the presence of a biological fluid and concurrently therewith delivers drug 16 to a drug receiving patient. Coat 26 provides instant therapy and it essentially overcomes the time required for the drug to be delivered from the dosage form.

Dosage form 10, as provided by this invention, and as seen in the above drawing figures can be manufactured for administering drug 16 by the oral route, and in another embodiment, dosage form 10 comprising exterior and interior drug 16 can be sized and shaped for administering drug 16 by the sublingual and buccal routes. The sublingual and buccal routes can be used for quicker therapy and they can be used when a smaller dose of drug 16 is needed for therapy. The buccal and sublingual routes can be used as a by-pass of the first pass of hepatic metabolism of drug 16. The sublingual or buccal routes can be used for administering the first dose of drug, followed by permitting dosage form 10 to enter the gastrointestinal tract for subsequent drug delivery.

Dosage form 10, when manufactured as an osmotic, controlled-release dosage form, comprises at least one passageway 13, or more than one passageway 13. The expression "at least one passageway" includes aperture, orifice, bore, pore, porous element through which the drug can be pumped, diffuse, travel or migrate, hollow fiber, capillary tube, porous overlay, porous insert, microporous member, porous composition, and the like. The expression also includes a material that erodes or is leached from wall 12 in the fluid environment of use to produce at least one passageway in dosage form 10. Representative material suitable for forming at least one passageway, or a multiplicity of passageways, includes an erodible poly(glycolic) acid or poly(lactic) acid member in the wall; a gelatinous filament; poly(vinyl alcohol); leachable materials such as fluid removable pore forming polysaccharides, salts, or oxides, and the like. A passageway or a plurality of passageways can be formed by leaching a material such as sorbitol, sucrose, lactose, fructose, or the like, from the wall to provide an osmotic dimensioned pore-passageway. The passageway can have any shape such as round, triangular, square, elliptical, and the like, for assisting in the metered release of drug from dosage form 10. Dosage form 10 can be constructed with one or passageways in spaced apart relation on one or more than a single surface of a dosage form. Passageways and equipment for forming passages are disclosed in U.S. Pat. Nos. 3,845,770 and 3,916,899 by Theeuwes and Higuchi; in U.S. Pat No. 4,063,064 by Saunders et al; and in U.S. Pat. No. 4,088,864 by Theeuwes et al. Osmotic passageways comprising controlled-drug releasing dimension, sized, shaped and adapted as a drug releasing pore formed by aqueous leaching to provide a drug-releasing pore of controlled osmotic release rate are disclosed in U.S. Pat. No. 4,200,098 by Ayer and Theeuwes; and in U.S. Pat. No. 4,285,987 by Ayer and Theeuwes.

Wall 12 of osmotic dosage form 10 can be formed in one technique using the air suspension procedure. This procedure consists in suspending and tumbling the compressed drug-push core laminate in a current of air and wall forming composition until a wall is applied to the drug-push compartment. The air suspension procedure is well-suited for independently forming the wall. The air suspension procedure is described in U.S. Pat. No. 2,799,241; J. Am. Pharm. Assoc., Volume 48, pages 451 to 454, (1959); and ibid, Volume 49, pages 82 to 84, (196). Osmotic dosage forms can also be coated with a wall forming composition in a Wurster ® air suspension coater, using methylene dichloride-methanol cosolvent, 80:20, wt:wt, an ethanol-water, or acetone-water cosolvent, 95:5 wt:wt using 2.5 to 4% solids. The Aeromatic ® air suspension coater using a methylene dichloride-methanol cosolvent, 80:20 wt:wt, also can be used for applying the wall. Other wall forming techniques such as pan coating system, where wall forming compositions are deposited by successive spraying of the composition on the drug-push compartment, accompanied by tumbling in a rotating pan. Finally, the wall coated compartments are dried in a forced air over at 30°C. to 50°C. for up to a week to free dosage form 10 of solvent. Generally, the walls formed by these techniques have a thickness of 2 to 30 mils with a presently preferred thickness of 4 to 10 mils.

Dosage form 10 of the invention is manufactured by standard manufacturing techniques. For example, in one manufacture the beneficial drug and other ingredients comprising the drug layer facing the exit means are blended and pressed into a solid layer. The drug and other ingredients can be blended with a solvent and mixed into a solid or semisolid formed by conventional methods such a ball-milling, calendering, stirring or rollmilling and then pressed into a preselected shape. The layer possesses dimensions that correspond to the internal dimensions of the area the layer is to occupy in the dosage form and it

also possesses dimensions corresponding to the second layer for forming a contacting arrangement therewith. Next, the push layer, is placed in contact with the drug layer. The push layer is manufactured using techniques for providing the drug layer. The layering of the drug layer and the push layer can be fabricated by conventional press-layering techniques. Finally, the two layer compartment forming members are surrounded and coated with an outer wall. A passageway is laser, leached, or mechanically drilled through the wall to contact the drug layer, with the dosage form optically oriented automatically by the laser equipment for forming the passageway on the preselected surface when a laser is used for forming the passageway.

In another manufacture, the dosage form is manufactured by the wet granulation technique. In the wet granulation technique, for example, the drug and the ingredients comprising the drug layer are blended using an organic solvent, such as isopropyl alcohol-ethylene dichloride 80:20 v:v (volume:volume) as the granulation fluid. Other granulating fluid such as denatured alcohol 100% can be used for this purpose. The ingredients forming the drug layer are individually passed through a 40 mesh screen and then thoroughly blended in a mixer. Next, other ingredients comprising the drug layer are dissolved in a portion of the granulation fluid, such as the cosolvent described above. Then the latter prepared wet blend is slowly added to the drug blend with continual mixing in the blender. The granulating fluid is added until a wet blend is produced, which wet mass then is forced through a 20 mesh screen onto oven trays. The blend is dried for 18 to 24 hours at 30°C. to 50°C. The dry granules are sized then with a 20 mesh screen. Next, a lubricant is passed through an 80 mesh screen and added to the dry screen granule blend. The granulation is put into milling jars and mixed on a jar mill for 1 to 15 minutes. The push layer is made by the same wet granulation

techniques. The compositions are pressed into their individual layers in a Manesty ® press-layer press.

Another manufacturing process that can be used for providing the compartment-forming composition layers comprises blending the powered ingredients for each layer independently in a fluid bed granulator. After the powered ingredients are dry blended in the granulator, a granulating fluid, for example, poly(vinyl-pyrrolidone) in water, or in denatured alcohol, or in 95:5 ethyl alcohol /water, or in blends of ethanol and water is sprayed onto the powders. Optionally, the ingredients can be dissolved or suspended in the granulating fluid. The coated powders are then dried in a granulator. This process granulates all the ingredients present therein while adding the granulating fluid. After the granules are dried, a lubricant such as stearic acid or magnesium stearate is added to the granulator. The granules for each separate layer are pressed then in the manner described above.

The dosage form of the invention is manufactured in another manufacture by mixing a drug with composition forming ingredients and pressing the composition into a solid lamina possessing dimensions that correspond to the internal dimensions of the compartment. In another manufacture the drug and other drug composition-forming ingredients and a solvent are mixed into a solid, or a semisolid, by conventional methods such as ballmilling, calendering, stirring or rollmilling, and then pressed into a preselected layer forming shape. Next, a layer of a composition comprising an osmopolymer and an optional osmagent are placed in contact with the layer comprising the drug. The layering of the first layer comprising the drug and the second layer comprising the osmopolymer and optional osmagent composition can be accomplished by using a conventional layer press technique. The wall can be applied by molding, spraying or dipping the pressed bilayer's shapes into wall forming

materials. Another and presently preferred technique that can be used for applying the wall is the air suspension coating procedure. The procedure consists in suspending and tumbling the two layers in current of air until the wall forming composition surrounds the layers. The air suspension procedure is described in U.S. Pat. No. 2,799,241; J. Am. Pharm. Assoc., Vol. 48 pp 451-454 (1979); and, ibid, Vol. 49, pp 82-84 (1960). Other standard manufacturing procedures are described in Modern Plastics Encyclopedia, Vol 46, pp 62-70 (1969); and in Pharmaceutical Science, by Remington, 14th Ed., pp 1626-1678 (1970), published by Mack Publishing Co., Easton, Pa.

Exemplary solvents suitable for manufacturing the wall, the laminates and laminae include inert inorganic and organic solvents final laminated wall. The solvents broadly include members selected for the group consisting of aqueous solvents, alcohols, ketones, esters, ethers, aliphatic hydrocarbons, halogenated solvents, cyclaliphatics, aromatics, heterocyclic solvents and mixtures thereof. Typical solvents include acetone, diacetone, alcohol, methanol, ethanol, isopropyl alcohol, butyl alcohol, methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, methyl propyl ketone, n-hexane, n-heptaene ethylene glycol monoethyl ether, ethylene glycol monoethyl acetate, methylene dichloride, ethylene dichloride, propylene dichloride, carbon tetrachloride, chloroform, nitroethane, nitropropane, tetrachoroethan, ethyl ether, isopropyl ether, cyclohexane, cyclooctane, benzene, toluene, naphtha, tetrahydrofuran, diglyme, aqueous and nonaqueous mixtures thereof, such as acetone and water, acetone and methanol, acetone and ethyl alcohol, methylene dichloride and methanol, and ethylene dichloride and methanol.

DETAILED DISCLOSURE OF EXAMPLES OF THE INVENTION

The following examples are merely illustrative of the present invention and they should not be considered as limiting the scope of the invention in any way as these examples and other equivalents thereof will become apparent to those versed in the art in the light of the present disclosure, the drawings and accompanying claims.

EXAMPLE 1

A dosage form adapted for delivering a drug in a therapeutic range is manufactured as follows: first a displacement or push layer is prepared by blending and passing through a stainless steel sizing screen having a mesh opening of 420 microns 587.5 grams of sodium carboxymethylcellulose having a degree of polymerization of approximately 3,200 and a degree of substitution of 0.7 carboxymethyl groups per anhydroglucose unit, 300 grams of powdered sodium chloride, 50 grams of hydroxypropylcellulose having a molecular weight of approximately 60,000 grams per mole, and 50 grams of hydroxypropylmethylcellulose having an average methoxyl content of 29 weight percent and an average hydroxypropyl content of 10 weight percent and an average molecular weight of approximately 11,300 grams per mole. Next 10 grams of red ferric oxide were passed through a sizing screen having openings of approximately 250 microns. The resulting powders were mixed in a planetary mixer to a uniform blend. The resulting blend was wet granulated by adding with stirring anhydrous ethyl alcohol until, a cohesive mass was formed. This mass was passed through a sizing screen having openings of approximately 840 microns, forming coated displacement particles, which were an dried overnight at ambient temperature and humidity. The dried particles were then passed again through the 840 micron sizing screen. Next 2.5 grams of

magnesium stearate, which had been previously sized through a mesh having 180 micron openings, were tumble mixed into the coated particles.

A composition comprising a drug of the structural formula was prepared as follows: first, a drug composition was prepared by passing 840 grams of venlafaxine hydrochloride, 100 grams of hydroxypropylcellulose having a molecular weight of approximately 60,000 grams per mole, and 50 grams of polyvinylpyrrolidone having a molecular weight of approximately 40,000 grams per mole, were passed through a sizing having openings of approximately 420 microns, and mixed in a planetary mixer to yield a uniform blend. Then, anhydrous ethyl alcohol was added to the mixture with stirring to produce a cohesive damp mass. The resulting damp mass was sized through a sieve having an opening of 840 microns, producing coated venlafaxine drug, which was air dried overnight. The resulting dried coated venlafaxine drug was passed again through the sizing screen having an 840 micron opening. Next, 10 grams of magnesium stearate, sized to 180 microns, was tumble mixed into the blend.

Next, the displacement-push composition and the drug composition were formed into a bilayer core as follows: first, 87 mg of the drug composition was placed in a 9/32 inch round die cavity and lightly tamped with a standard concave round tooling to form a slightly cohesive layer. Then, 70 mg of push composition was added to die and the and the resulting fill was compressed with a final force of 2 tons, thereby forming a two layer cores.

The bilayer cores were placed next in a coating pan having a 12 inch diameter and they were coated with a wall-forming solution. The wall-forming solution was prepared by dissolving 380 grams of cellulose

acetate having an acetyl content of 39.8 weight percent in 7,220 grams of acetone. In a separate mixing vessel, 20 grams of polyethylene glycol having a molecular weight of approximately 3,350 grams per mole were dissolved in approximately 380 grams of purified water. The two solutions were mixed to form the wall-coating solution which was spray coated onto the cores until about 20 mg of wall composition was deposited on the surfaces of the bilayer core.

A delivery exit port was formed across the wall by drilling an exit port, centered on the face of the dosage form on the drug composition side of the dosage form. The resulting dosage form was placed in simulated physiological fluid at 37°C., and the dosage form delivered a dose of 73 mg of venlafaxine hydrochloride at a controlled, zero rate over an extended duration of 15 hours.

EXAMPLE 2

The procedure of Example 1 was followed with the manufacturing procedures as set forth, except that the drug composition comprises 890 grams of venlafaxine hydrochloride, 100 grams of hydroxypropylcellulose, and 10 grams of magnesium stearate. The resulting dosage form released in simulated intestinal fluid 77 mg of venlafaxine hydrochloride at a zero-order rate over an extended duration of 16 hours.

EXAMPLE 3

The procedure of Example 1 was followed with all manufacturing steps as described, except that the drug composition consists of 650.0 grams of venlafaxine hydrochloride, 240.0 grams of maltodextrin having an average molecular weight of approximately 1800 grams per mole and an average degree of polymerization of 11.1, 80.0 grams of

hydroxypropyl cellulose, 20.0 grams of polyvinyl pyrrolidone, and 10.0 grams of magnesium stearate. The resulting dosage form was tested in artificial intestinal fluid, the dosage form delivered a dose of 57 mg of venlafaxine hydrochloride at zero order rate over a period of 15 hours.

EXAMPLE 4

The procedure of Example 1 was repeated with the manufacture as previously set-forth, except that the drug composition consists of 840.0 grams of venlafaxine hydrochloride, 150.0 grams of polyethylene oxide having an average molecular weight of approximately 100,000 grams per mole, and 10.0 grams of magnesium stearate. The wall weight weighed approximately 25 mg. The resulting dosage forms were tested in simulated intestinal fluid, and they released a dose of 73 mg of venlafaxine hydrochloride at controlled rate over an extended period of 20 hours.

EXAMPLE 5

The compositions were manufactured as in Example 1. The process of manufacture was the same except that the push layer manufactured was prepared in a fluid bed aqueous-based granulation process. This was accomplished by sizing the sodium carboxymethyl cellulose, the sodium chloride, the hydroxypropyl cellulose, and red ferric oxide through a screen having openings of 420 microns. The resulting powders were charged into a fluid bed granulation column and binder solution consisting of the hydroxypropyl methylcellulose at a 5 percent solids concentration in water was sprayed on, thereby forming the granules for the push layer.

EXAMPLE 6

The compositions and processes followed in this example were the same as in Example 1 except the push consisted of 740.0 grams polyethylene oxide with an average molecular weight of approximately 5 million grams per mole, 200.0 grams of sodium chloride, 50.0 grams of hydroxypropyl methyl cellulose having average molecular weight of approximately 11,300 per mole, 5.0 grams of red ferric oxide, and 5.0 grams of magnesium stearate.

DESCRIPTION OF METHOD OF PERFORMING THE INVENTION

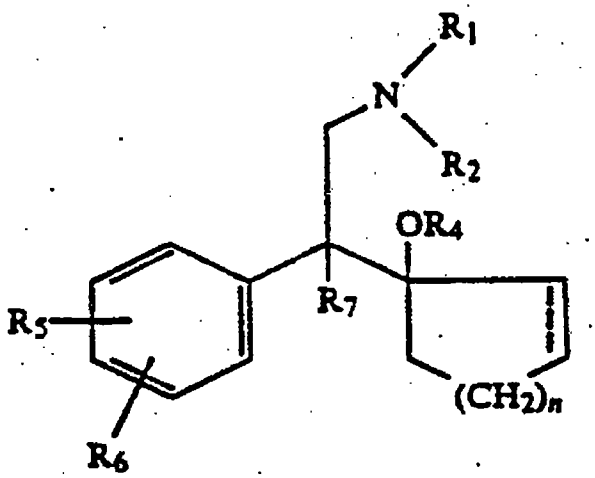
Additional embodiments of the invention pertains to a method for delivering a drug embraced by the structural formula of this invention for its intended therapy. One embodiment pertains to a method for delivering a drug of the formula by administering a dosage form comprising 0.5 mg to 750 mg of the drug from a dosage form selected from sustained-release and controlled-release dosage forms in a therapeutically responsive dose over an extended period of time. Another embodiment of the invention pertains to a method for delivering a drug of the formula disclosed in this invention, to the gastrointestinal tract of a human in need of this therapy, wherein the method comprises the steps of: (A) admitting orally into the gastrointestinal tract of the human a dosage form comprising: (1) a non-toxic wall composition comprising means for imbibing an external aqueous fluid through the wall into the dosage form, which wall surrounds and defines; (2) an internal compartment; (3) a drug composition comprising a drug of the formula in the compartment comprising a dosage unit amount of said drug; (4) a push composition in the compartment for pushing the drug composition from the compartment; (5) at least one exit means in the wall for delivering the drug from the dosage form; (B) imbibing fluid through the wall into the

compartment thereby causing the composition to form a deliverable dosage form and concomitantly causing the push composition to expand and push the drug composition through the exit means from the dosage form; and (C) deliver the therapeutic drug in a therapeutically effective amount at a controlled rate over an extended period of time to the patient in need of said therapy. The method also comprising dispensing a dose amount of said drug from an instant release exterior dosage amount of drug to the patient for providing instant anti-depressant therapy.

Inasmuch as the foregoing specification comprises preferred embodiments of the invention, it is understood that variations and modifications may be made herein, in accordance with the inventive principles disclosed, without departing from the scope of the invention.

We claim:

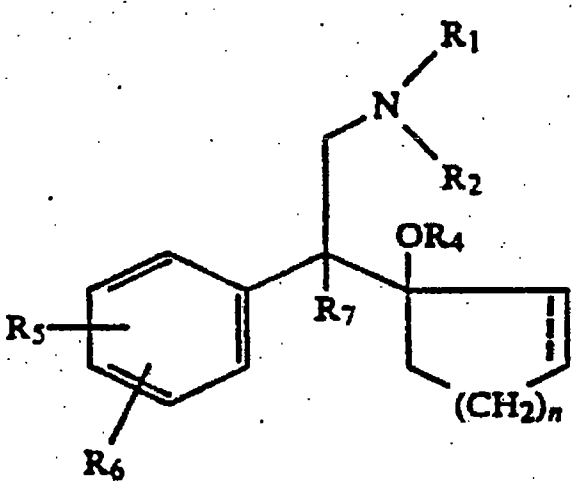
1. A therapeutic composition comprising 0.5 mg to 750 mg of a drug of the formula:



wherein the dotted line represents an unsaturation or a cycloalkenyl group; R_1 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbon atoms; R_2 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbon atoms; R_4 is a member selected from the group consisting of hydrogen, alkyl of 1 to 6 carbon atoms, formyl, and alkanoyl of 2 to 7 carbon atoms; R_5 and R_6 are independently a member selected from the group consisting of hydrogen, hydroxyl, an alkyl of 1 to 6 carbon atoms, an alkoxy of 1 to 6 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, nitro, alkylmercapto of 1 to 6 carbon atoms, amino, alkylamino of 1 to 6 carbon atoms in which each alkyl group comprises 1 to 6 carbon atoms, alkanamide of 2 to 7 carbon atoms, halo, and trifluoroethyl, R_7 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbons, and n is one of the integers 0, 1, 2, 3, and 4, and a pharmaceutically acceptable addition

salt; and wherein the drug of the formula is blended with a poly(alkylene oxide) polymer.

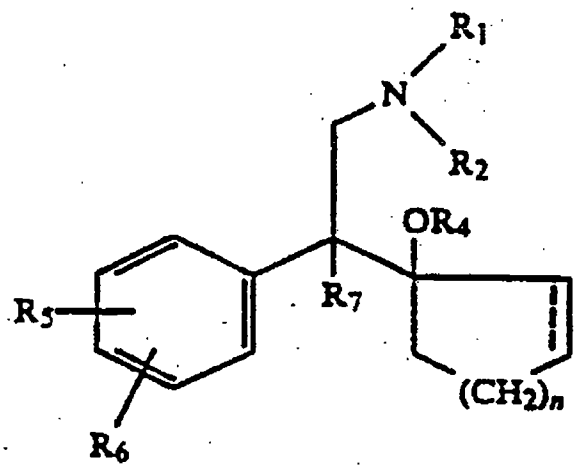
2. A therapeutic composition comprising 0.5 mg to 750 mg of a drug of the formula;



wherein the dotted line represents an unsaturation or a cycloalkenyl group; R_1 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbon atoms; R_2 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbon atoms; R_4 is a member selected from the group consisting of hydrogen, alkyl of 1 to 6 carbon atoms, formyl, and alkanoyl of 2 to 7 carbon atoms; R_5 and R_6 are independently a member selected from the group consisting of hydrogen, hydroxyl, an alkyl of 1 to 6 carbon atoms, an alkoxy of 1 to 6 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, nitro, alkylmercapto of 1 to 6 carbon atoms, amino, alkylamino of 1 to 6 carbon atoms in which each alkyl group comprises 1 to 6 carbon atoms, alkanamido of 2 to 7 carbon atoms, halo, and trifluoroethyl; R_7 is a member selected from the group

consisting of hydrogen and alkyl of 1 to 6 carbons and n is one of the integers 0, 1, 2, 3, 4, and a pharmaceutically acceptable addition salt; and wherein the drug of the formula is blended with a cellulose polymer.

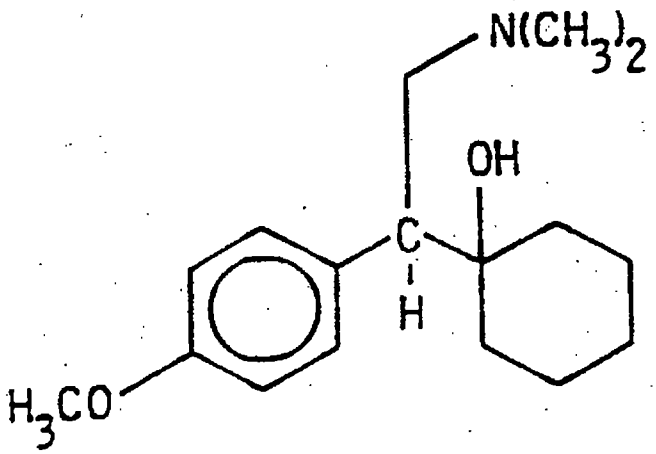
3. A therapeutic composition comprising 0.5 mg to 750 mg of a drug of the formula:



wherein the dotted line represents an unsaturation or a cycloalkenyl group; R_1 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbon atoms; R_2 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbon atoms; R_4 is a member selected from the group consisting of hydrogen, alkyl of 1 to 6 carbon atoms, formyl, and alkanoyl of 2 to 7 carbon atoms; R_5 and R_6 are independently a member selected from the group consisting of hydrogen, hydroxyl, an alkyl of 1 to 6 carbon atoms, an alkoxy of 1 to 6 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, nitro, alkylmercapto of 1 to 6

carbon atoms, amino, alkylamino of 1 to 6 carbon atoms in which each alkyl group comprises 1 to 6 carbon atoms, alkanamido of 2 to 7 carbon atoms, halo, and trifluoroethyl, R_7 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbons, and n is one of the integers 0, 1, 2, 3, and 4; and a pharmaceutically acceptable addition salt; and wherein the drug of the formula is blended with a maltodextrin polymer.

4. A dosage form for administering a drug to an environment of use, wherein the dosage form comprises a drug of the formula:



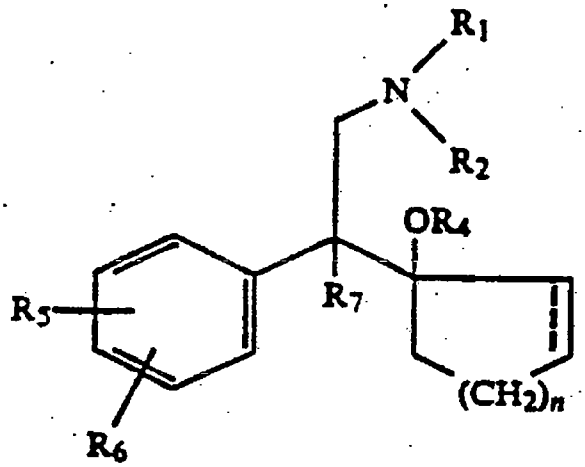
which dosage form comprises a member selected from the group consisting of a sustained-release dosage form and a controlled release dosage form, and wherein said dosage form comprises means for storing the drug and means for releasing the drug over an extended period of time.

5. A dosage form for the oral delivery of a drug to an environment of use, wherein the dosage form comprises:

(a) a wall comprising at least in part a composition permeable to the passage of fluid, which wall surrounds:

(b) a compartment;

(c) a drug composition in the compartment comprising a drug of the formula:



wherein the dotted line represents a member selected from the group consisting of an unsaturation and cycloalkenyl group; R_1 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbon atoms; R_2 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbon atoms; R_4 is a member selected from the group consisting of hydrogen, alkyl of 1 to 6 carbon atoms, formyl, and alkanoyl of 2 to 7 carbon atoms; R_5 and R_6 are independently a member selected from the group consisting of hydrogen, hydroxyl and alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, alknaoyloxy of 2 to 7 carbon atoms, nitro, alkylmercapto of 1 to 6 carbon atoms, amino, alkylamino of 1 to 6 carbon atoms, alkanamido of 2 to 7 carbon atoms, halo and trifluoroethyl; R_7 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbons; an n is 0 to 4; and

(d) a displacement in the compartment comprising a composition comprising an osmotically active compound; and,

(e) an exit passageway in the dosage form for delivering the drug composition from the dosage form.

6. A dosage form for the oral delivery of the drug to an environment of use according to claim 5, wherein the drug is 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]-cyclohexanol.

FIG.1

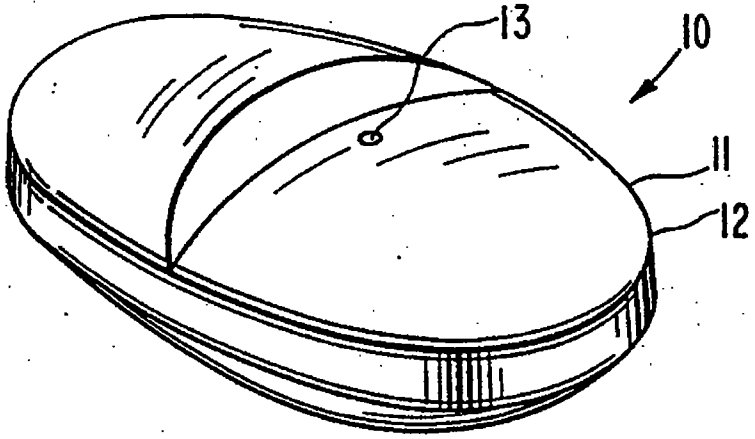


FIG.2

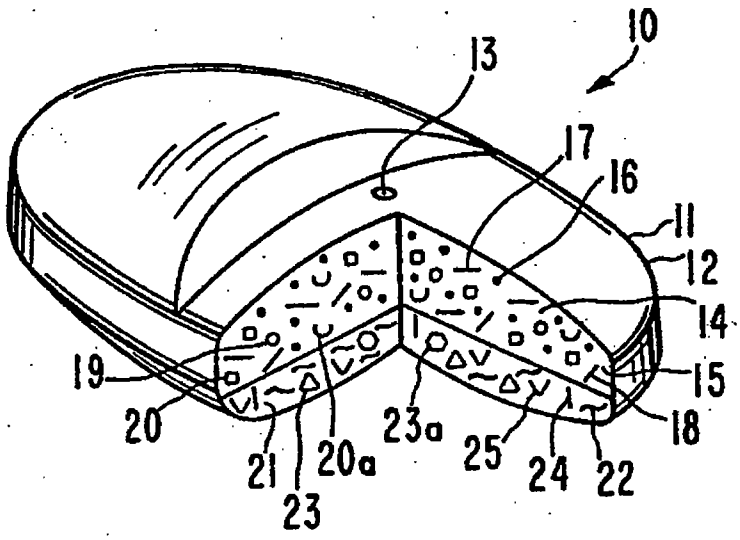


FIG.3

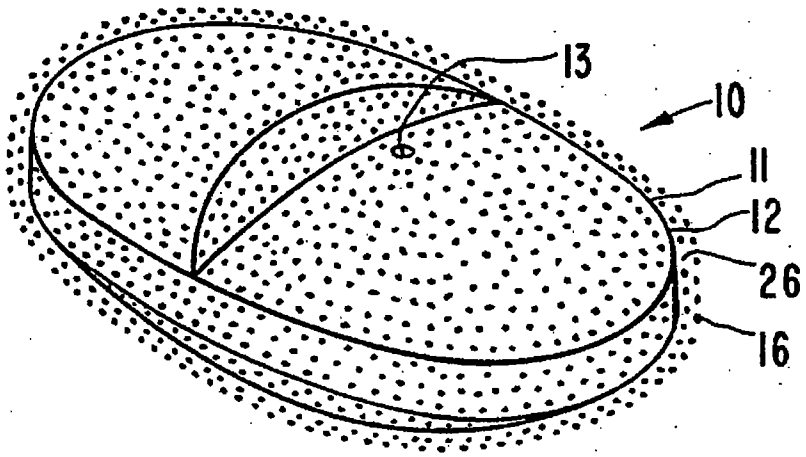


EXHIBIT 23
REDACTED

Exhibit 24

US006440457B1

(12) **United States Patent**
Edgren et al.

(10) **Patent No.: US 6,440,457 B1**
(45) **Date of Patent: Aug. 27, 2002**

(54) **METHOD OF ADMINISTERING ANTIDEPRESSANT DOSAGE FORM**

(75) Inventors: **David Emil Edgren**, El Granada; **Gurdish Kaur Bhatti**; **Zahedeh Hatamkhani**, both of Fremont; **Patrick S. L. Wong**, Palo Alto, all of CA (US)

(73) Assignee: **Alza Corporation**, Mountain View, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **08/068,480**

(22) Filed: **May 27, 1993**

(51) **Int. Cl.**[7] **A61K 9/22**; A61K 9/52; A61K 31/137; A61P 25/24

(52) **U.S. Cl.** **424/468**; 424/457; 424/473; 514/964; 514/654

(58) **Field of Search** 424/473, 468, 424/457; 514/964, 654

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Primary Examiner—Edward J. Webman
(74) *Attorney, Agent, or Firm*—Robert R. Neller

(57) **ABSTRACT**

The invention pertains to a dosage form **10** and to administering an antidepressant medicament **16** for an extended period of time in a rate-known dose.

1 Claim, 1 Drawing Sheet

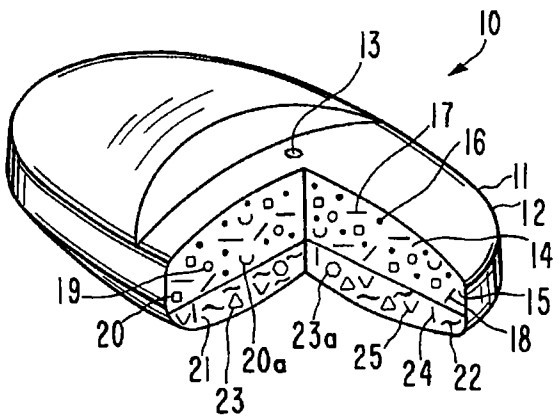


FIG. 1

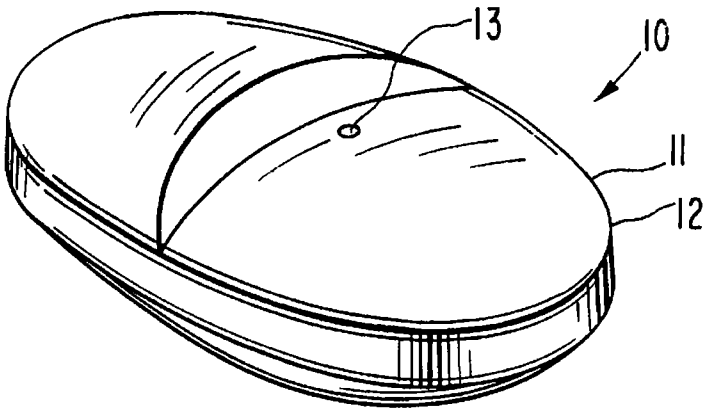


FIG. 2

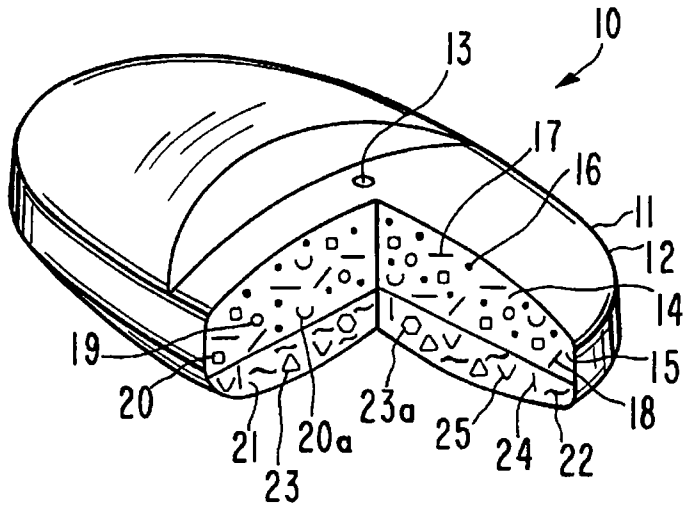
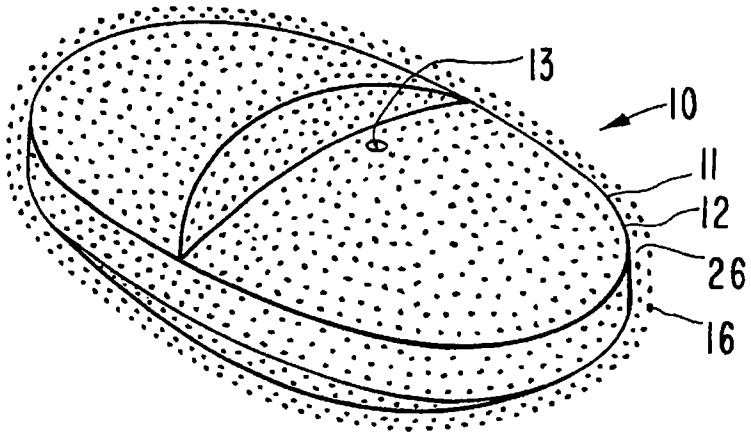


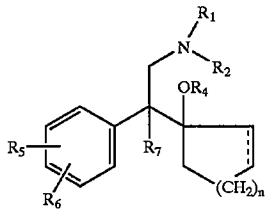
FIG. 3



METHOD OF ADMINISTERING ANTIDEPRESSANT DOSAGE FORM

FIELD OF THE INVENTION

This invention pertains to a controlled-release dosage form comprising a compound of the following structural formula:



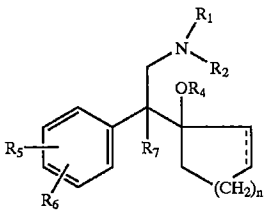
useful for antidepressant therapy. The invention concerns also a method useful for antidepressant therapy by administering the controlled-release dosage form comprising the compound of the formula.

BACKGROUND OF THE INVENTION

The primary goal of drug administration is to provide a therapeutic dose of drug in the body to achieve a desired blood concentration, and then maintain the desired drug blood concentration. The prior art, in attempts to obtain the desired therapeutic effect, often used different dosage forms or programs. One dosage program consists of a single dosing of the drug from a conventional capsule or tablet that produced a rapid rise followed by an immediate decline of the drug blood level versus time. The single dosing does not maintain the drug within a therapeutic range for an extended period of time, but exhibits of a short duration of action due to the inability of the conventional dosage form to provide drug delivery over time.

Another prior art dosing program used to obtain and to achieve drug blood levels consists in administering the drug repetitively using conventional dosage forms at various dosing intervals, as in multiple-dose therapy. In administering a drug according to the multiple-dose therapy, the drug blood level reached and the time required to reach that level depends on the dose and the dosing interval. There are, however, several potential problems inherent in multiple dose therapy. For example, if the dosing interval is not appropriate for the biological half-life of the drug, large peaks and valleys may result in the drug blood levels. Also, the drug blood level may not be within the therapeutic range at sufficiently early times, an important consideration for many disease states. And too, patient noncompliance with the multiple dosing regimen can result in a failure of this approach, especially as a drug in circulation surges to a high each time the drug is administered followed by a decline in drug concentration in the blood and in body compartments. Thus, a graph of drug in circulation following a dosage program of several doses, has an appearance of a series of peaks:, which may surpass the toxic threshold. Then, each time the blood levels decreases into valleys, below a critical level needed to achieve a desired therapeutic effect, that effect may not be obtainable in the blood and body. Conventional dosage forms and their mode of operation are discussed in *Remington's Pharmaceutical Sciences,* 18th Edition, pages 1676 to 1686, (1990), Mack Publishing Co.; *The Pharmacological Basis of Therapeutics,* 7th Edition, page 7 (1985) published by MacMillian Publishing Co., and in U.S. Pat. Nos. 3,598,122 and 3,598,123 both issued to Zaffaroni.

A critical need exists for a controlled-rate dosage form for administering the drug of the formula:



which drug is presently administered in conventional dosage forms including tablets, capsules, elixirs and suspensions. These conventional dosage forms produce the peaks and valleys drug pattern presented above and they do not provide for controlled-rate therapy over an extended period of time. The drug of the formula is dosed twice or thrice a day now because of its elimination half-life of three to five hours. This pattern of dosing indicates the need for a controlled-release dosage form that can administer the drug at a controlled rate over an extended time to provide constant therapy and thereby eliminate the need for multiple dosing. The drugs of the structural formula are known in U.S. Pat. Nos. 4,535,186; 4,611,078; and 4,761,501 all issued to Husbands, Yardley and Muth.

The prior art provided controlled-release dosage forms that can continuously over time administer a drug for controlled-rate therapy. For example, in U.S. Pat. No. 4,327,725 issued to Cortese and Theeuwes and in U.S. Pat. Nos. 4,612,008; 4,765,989; and 4,783,337 issued to Wong, Barclay, Deters, and Theeuwes. The dosage forms disclosed in these patents provide a drug at a constant rate for effecting a therapeutic range for preferred therapy. The dosage forms of the patents provide a therapeutic range and avoids delivering the drug in excess in a toxic range with its accompanying side-effects. The dosage forms of the patents in providing a controlled dose in a therapeutic range also avoids delivering the drug in an ineffective dose in an ineffective range.

The dosage forms presented immediately above operate successfully for their intended use and they can deliver many drugs indicated for good therapy. The drugs of the above structural formula, however, possess properties such as a high solubility of 570 mg per ml at a body temperature of 37° C. that can lead to a premature release of the drug from the dosage form. During operation of the dosage forms, the convection motion of the imbibed fluid, and the hydrostatic pressure of the imbibed fluid coupled with the high solubility can result in the premature release of the drugs of the formula.

It is immediately apparent in the light of the above presentation that an urgent need exists for a dosage form endowed with controlled-release delivery for delivering the drugs embraced by the structural formula. The need exists for the dosage form for delivering the drug at a controlled dose in a therapeutic range while simultaneously providing the intended therapy. It will be appreciated by those versed in the dispensing art, that such a dosage form that can administer the drug in a controlled-rate dose over time, would, represent an advancement and a valuable contribution to the art.

OBJECTS OF THE INVENTION

Accordingly, in view of the above presentation, it is an immediate object of this invention to provide a dosage from

that possesses controlled-release delivery for providing a dosage form for administering a drug of the structural formula.

Another object of the present invention is to provide a dosage form for administering the drug of the formula in a controlled-rate dose in a therapeutic range over a prolonged period of time.

Another object of the present invention is to provide a dosage form that can deliver the drug of the formula essentially-free of a premature release from the dosage form.

Another object of the present invention is to provide a drug delivery controlled-release system that can deliver a drug for maintaining constant drug levels in the blood thereby functioning as a prolonged release system.

Another object of the present invention is to provide drug delivery sustained-release system that provides slow release of the drug over an extended period of time optionally in a therapeutic range.

Another object of the present invention is to provide a dosage form that substantially reduces and/or substantially eliminates the unwanted influences of a gastrointestinal environment of use and still provides controlled drug administration.

Another object of the present invention is to provide an improvement in a dosage form for administering a drug embraced by the structural formula and its pharmaceutically acceptable salt, wherein the improvement comprises delivering the drug in a controlled-release rate from the dosage form for improved and known therapy.

Another object of the invention is to provide a once-a-day controlled-release dosage form to deliver the drug of the structural formula orally to a patent in need of therapy.

Another object of the invention is to provide a method for administering a drug of the formula by orally administering the drug in a controlled rate dose per unit dose over an extended time to an animal in need of therapy.

Another object of the present invention is to provide a method for administering a drug of the formula in a therapeutic range while simultaneously substantially-avoiding a toxic range and an infective range.

Another object of the present invention is to provide a therapeutic composition comprising a drug of the structural formula blended with a drug-composition forming polymer.

Another object of the invention is to provide a therapeutic composition comprising a member selected from the group consisting of venlafaxine and its pharmaceutically acceptable additional salt and a pharmaceutically acceptable polymer carrier for venlafaxine and its acceptable salts.

Other objects, feature, and advantages of the invention will more apparent to those versed in the dispensing arts from the following detailed specification, taken in conjunction with the drawings and the accompanying claims.

BRIEF DESCRIPTION OF THE DRAWINGS

In the drawing figures, which are not drawn to scale, but are set forth to illustrate various embodiments of the invention, the drawing figures are as follows:

Drawing FIG. 1 is a general view of a dosage form provided by the invention, which dosage form is designed and shaped for oral administration, and for a drug delivery in a controlled-rate dose in the gastrointestinal tract;

Drawing FIG. 2 is an opened view of the dosage form of drawing FIG. 1 for depicting the structure of the dosage form and the composition member contained inside the dosage form; and

Drawing FIG. 3 is a view of a dosage form that depicts an external, instant-release of drug of the structural formula coated on the exterior surface of the dosage form.

In the drawing figures, and in the specification, like parts in related figures are identified by like numbers. The terms appearing earlier in the specification and in the description of the drawing figures, as well as embodiments thereof, are further described elsewhere in the disclosure.

DETAILED DESCRIPTION OF THE DRAWINGS

Turning now to the drawing figures in detail, which drawing figures are examples of dosage forms provided by this invention, and which examples are not to be construed as limiting, one example of a dosage form is seen in drawing FIG. **1**. In drawing FIG. **1**, a dosage form **10** is seen comprising a body member **11**, which body **11** comprises wall **12**, that surrounds and forms an internal area, not seen in drawing FIG. **1**. Dosage form **10** comprises at least one exit port **13** for connecting the exterior with the interior of dosage form **10**.

The dosage form **10** of drawing FIG. **1** illustrates a controlled-release dosage form manufactured as an osmotic dosage form that delivers a drug by osmotic action over an extended period of time. The dosage form comprising controlled-release properties embraced by this invention are successful at maintaining substantially constant drug levels in the blood or in a tissue. The dosage forms within the mode and manner of this invention comprises also sustained-release dosage forms. The sustained-release dosage forms releases the drug and provide drug levels in the blood or target tissue within a therapeutic range over an extended period of time. The invention embraces additionally prolonged release dosage forms. The prolonged release dosage form denotes extended duration of drug delivery action over that achieved by conventional drug delivery.

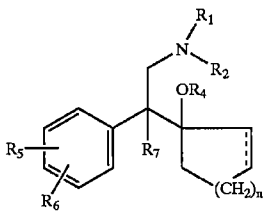
In drawing FIG. **2**, dosage form **10** of FIG. **1** is seen in opened section. In drawing FIG. **2**, dosage form **10** comprises a body **11**, a wall **12** that surrounds and defines an internal compartment **14**. In drawing FIG. **2**, internal compartment **14** communicates through an exit passageway **13** with the exterior of dosage form **10**.

Wall **12** of dosage form **10** comprises totally or in at least a part of a composition that is permeable to the passage of an exterior fluid present in an environment of use, such as aqueous and biological fluids. Wall **12** is formed of nontoxic ingredients, is substantially impermeable to the passage of a drug and other ingredients present in compartment **14**. Wall **12** comprises a composition that is substantially inert, that is, wall **12** maintains its physical and chemical integrity during the drug dispensing life of a drug from dosage form **10**. The phrase, "maintaining its physical and chemical integrity," means wall **12** does not lose its structure and it does not change during the dispensing life of dosage form **10**, except for possible leaching of one or more exit **13** passageway formed during operation of dosage form **10** or for leaching a water-soluble flux enhancers blended into wall **12**. Wall **12** comprises a material that does not adversely affect an animal, a human or any other components comprising the dosage form. Representative materials for forming wall **12**, are in one embodiment, a cellulose ester polymer, a cellulose ether polymer and a cellulose esterether polymer. These cellulosic polymers have a degree of substitution. D.S., on the anhydroglucose unit, from greater than 0 up to 3 inclusive. By degree of substitution is meant the average number of hydroxyl groups originally present on the anhydroglucose unit comprising the cellulose polymer that are replaced by a

substituting group. Representative materials include a member selected from the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, mono-, di- and tricellulose alkanylates, mono-, di-, and tricellulose aroylates, and the like. Exemplary polymers include cellulose acetate having a D.S. up to 1 and an acetyl content up to 21%; cellulose acetate having a D.S. of 1 to 2 and an acetyl content of 21 to 35 %; cellulose acetate having a D.S. of 2 to 3 and an acetyl content of 35 to 44.8%, and the like. More specific cellulosic polymers include cellulose propionate having a D.S. of 1.8 and a propyl content of 39.2 to 45% and a hydroxyl content of 2.8 to 5.4%; cellulose acetate butyrate having a D.S. of 1.8, an acetyl content of 13 to 15% and a butyryl content of 34 to 39%; cellulose acetate butyrate having an acetyl content of 2 to 29%, a butyryl content of 17 to 53% and a hydroxyl content of 0.5 to 4.7; cellulose triacylates having a D.S. of 2.9 to 3 such as cellulose trivalerate, cellulose trilaurate, cellulose tripolmitate, cellulose trisuccinate, and cellulose trioctanoate; cellulose diacylates having a D.S. of 2.2 to 2.6 such as cellulose disuccinate, cellulose dipalmitate, cellulose dioctanoate, cellulose dipentanoate, co-esters of cellulose such as cellulose acetate butyrate and cellulose acetate propionate, and the like.

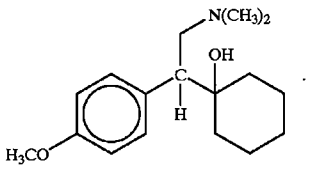
Additional polymers include ethyl cellulose of various degree of etherification with ethoxy content of from 40% to 55%, acetaldehyde dimethyl cellulose acetate, cellulose acetate ethyl carbamate, cellulose acetate methyl carbamate, cellulose acetate diethyl aminoacetate, semipermeable polyamides; semipermeable polyurethanes; semipermeable sulfonated polystyrenes; semipermeable cross-linked selective polymers formed by the coprecipitation of a polyanion and a polycation as disclosed in U.S. Pat Nos. 3,173,876, 3,276,586, 3,541,005; 3,541,006, and 3,546,142; semipermeable polymers as disclosed by Loeb and Sourirajan in U.S. Pat. No. 3,133,132; semipermeable lightly cross-linked polystyrene derivatives, semipermeable cross-linked poly (sodium styrene sulfonate); semipermeable cross-linked poly(vinylbenzyltrimethyl ammonium chloride); semipermeable polymers exhibiting a fluid permeability of 2.5×10^{-8} to 2.5×10^{-4}(cm^2/hr.atm) expressed per atmosphere of hydrostatic or osmotic pressure difference across the semipermeable wall. The polymers are known to the art in U.S. Pat. Nos. 3,845,770; 3,916,899; and 4,160,020; and in *Handbook of Common Polymers* by Scott, J. R. and Roff, W. J., 1971 published by CRC Press, Cleveland, Ohio.

Compartment **14** comprises a drug composition, identified as drug layer **15** which contains drug **16**, identified by dots. Drug **16** comprises a drug of the following structural formula:



wherein the dotted line represents optional unsaturation or a cycloalkenyl moiety; R_1 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbon atoms; R_2 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbon atoms; R_4 is a member selected from the group consisting of hydrogen, alkyl of 1 to 6 carbon atoms, formyl, and alkanoyl of 2 to 7 carbon atoms; R_5 and R_6 are independently a member selected from the group consisting of hydrogen, hydroxyl, an alkyd of 1 to 6 carbon atoms, an alkoxy of 1 to 6 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, nitro, alkylmercapto of 1 to 6 carbon atoms, amino, alkylamino of 1 to 6 carbon atoms in which each alkyl group comprises 1 to 6 carbon atoms, alkanamido of 2 to 7 carbon atoms, halo, and trifluoroethyl, R_7 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbons, and n is one of the integers 0, 1, 2, 3, and 4. The formula embraces also the pharmaceutically acceptable addition salts including a member selected from the group consisting of inorganic, organic, hydrochloric, hydrobromic, gluconic, fumaric, maleric, sulfonic, succinic, sulfuric, phosphoric, tartaric, acetic, proponic, citric, oxalic and similar pharmaceutically acceptable addition salts. The compounds are known in U.S. Pat. Nos. 4,535,186; 4,611, 078; 4,761,501; and 5,190,765.

The drugs of the structural formula are represented by the drug 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol of the structural formula:



The drug embraced by the formula possesses antidepressant properties. The drug in vitro prevents the neuronal uptake of serotonin, morepinephrine, and dopamine and it does not inhibit monoamine oxidase. The drug antagonizes reserpine-induced hypothermia and potentiates the effects of levodopa, and reduces histamine-induced corticotropin release and induces cyclicadenosine monophosphate subsensitivity after both acute and chronic administration. The drug possesses excellent antidepressant activity in humans. The therapeutic amount of drug **16** in dosage form **10** is 0.5 mg to 750 mg, with individual dosage forms comprising 2, 5, 10, 25, 40, 50, 75, 100, 150, 250, 300, 500, and 600 mg of drug **16** for administering in a single dose or in more then one dose over an extended period of 24 hours. The therapeutic properties of the drug embraced by the structural formula are reported in *Current Therapeutic Research,* Vol. 42, No. 5, pages 901 to 909 (1987).

Composition **15** comprising drug **16** may comprise a drug dispensing carrier and composition formulating member consisting of a member selected from the group consisting of 0 wt % to 25 wt % of a hydroxypropylalkylcellulose where alkyl consists of 1 to 7 carbons selected from the group consisting of methyl, ethyl, isopropyl, butyl, pentyl, and hexyl which cellulose member comprises a 9,000 to 1,250,000 molecular weight and is exemplified by hydroxypropylmethylcelluose, hydroxypropylethylcellulose, hydroxypropylisopropylcellulose, hydroxypropylbutylcellulose and hydroxypropylhexylcellulose represented by dashes **17**; a member selected from the group consisting of 0 wt % to 20 wt % hydroxylalkylcellulose where alkyl is 1 to 6 carbons including methyl, ethyl, propyl, butyl, pentyl, and hexyl which cellulose member comprises a 7,500 to 750,000 molecular weight and is exemplified by hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxyisopropylcellulose and

hydroxybutylcellulose as represented by slanted line **18**; a member selected from the group consisting of 0 wt % to 35 wt % of a vinyl-polymer having a 3,500 to 750,000 molecular weight represented by poly-n-vinylamide, poly-n-vinlycetamide, poly-n-vinylethylacetamide, poly-n-vinylmethylpropionamide, poly-n-vinyl ethylpropionamide, poly-n-vinylmethylisobutyramide, poly-n-vinyl-2-pyrrolidone, poly-n-vinypiperidone also known as polyvinylpyrrolidone and as poly-n-vinylpyrroledone, poly-n-vinylcaprolactam, poly-n-vinyl-5-methyl-2-pyrrolidone and poly-n-vinyl-3-methyl-2-pyrrolidone, and poly-n-vinylpyrrolidone copolymer with a member selected from the group consisting of vinyl acetate, vinyl alcohol, vinyl chloride, vinyl fluoride, vinyl butyrate, vinyl laurate and vinyl stearate represented by small circles **19**; and 0 wt %, where wt % is weight percent, 35 wt % of a maltodextrin polymer composition comprising the formula $(C_6H_{12}O_5)$, H_2O wherein n is 3 to 7,500 and the maltodextrin polymer comprises a 500 to 1,250,000 number average molecular weight represented by a small square **20**; as member selected from the group consisting of 0 wt % to 40 wt % of poly(etheylen oxide) having a molecular weight of 100,000 to 600,000 grams per mole, represented by half-circles **20***a*. Composition **15** optionally comprises from 0 to 4.5 wt % of a lubricant represented by magnesium stearate, calcium stearate or stearic acid. The total weight of all ingredients in composition **15** is equal to 100 wt %, weight percent.

Compartment **14** comprises a displacement composition or push layer **21**. Displacement composition **21** comprises a polymer member selected from the group consisting of a polymer possessing a repeating molecular unit $-(O-CH_2CH_2-)_n$ wherein n is a positive whole number of 50,000 to 300,000 as represented by a poly(alkylene oxide) comprising poly(ethylene oxide) seen as wavy line **22**; a maltodextrin polymer of the formula $(C_6H_{12}O_5)_n H_2O$ wherein n is 50 to 62,000 and comprises a 9,000 to 10,000,000 molecular weight and represented by triangle **23**; a carboxymethylcellulose polymer comprising a 10,000 to 5,000,000 molecular weight represented by alkali carboxymethylcellulose, sodium carboxymethylcellulose and potassium carboxymethylcellulose, ammonium carboxymethylcellulose, sodium carboxymethyl-2-hydroxyethylcellulose, sodium carboxymethylmethylcellulose, alkali carboxymethyl-hydroxypropylmethylcellulose, alkali carboxymethyl-2-hydroxyethylmethylcellulose, alkali carboxymethyl-2-hydroxybutylmethylcellulose, alkali carboxymethyl-2-hydroxyethyl-ethylcellulose and alkali carboxymethyl-2-hydroxypropylcellulose, where alkali is sodium and potassium and seen in drawing FIG. **2** as hexagonal **23***a*. The polymers in push layer **21** provide unforeseen operating advantages as the polymer maintains its chemical composition during operation as it imbibes an external aqueous fluid including biological fluid while simultaneously pushing the drug from the dosage form essentially-free of substantially mixing the drug composition with the push composition. The displacement composition **21** comprises optionally from 4 to 35 wt % of an osmotically active compound, also known as osmagent and represented by vertical line **24**. Representative of osmotically effective compounds comprises salts, oxides, esters that exhibit imbibition properties, carbohydrates and acids including a member selected from the group consisting of magnesium sulfate, magnesium chloride, sodium chloride, lithium chloride, potassium chloride, potassium sulfate, sodium sulfate, sodium sulfite, lithium sulfate, ammonium chloride, potassium lactate, mannitol, urea,: magnesium succinate, tartaric acid, raffinose, sorbitol, sucrose, fructose, and glucose. Displacement layer **21** optionally comprises 0.5 wt % to 30 wt % of a cellulose polymer **25** represented by the letter v. Representative of cellulose polymer **25** comprise a member selected from the group consisting of hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxypropylethylcellulose, hydroxypropylisopropylcellulose, hydroxypropylbutylcellulose, hydroxypropylpentylcellulose, and hydroxypropylhexylcellulose comprising a 9,000 to 225,000 molecular weight. The displacement composition optionally comprises 0 wt % to 5 wt % of lubricant stearic acid and, magnesium stearate, calcium oleate, oleic acid, and caprylic acid. The polymers are known in U.S. Pat Nos. 3,845,770; and 4,160,020; in *Handbook of Common Polymers* by Scott, J. R., and Roff, W. J., published by CRC Press, Cleveland, Ohio.

Dosage form **10**, a seen in drawing FIG. **3** depicts another preferred manufacture provided by the invention. Dosage form **10**, in drawing FIG. **3**, comprises an external coat on a the exterior surface of dosage form **10**. Coat **26** is a therapeutic composition comprising 10 mg to 150 mg of drug **16**, represented by dots **16**. Exterior coat **26** provides instant drug **16** for instant therapy. Drug **16** is blended with an aqueous-soluble composition comprising a carrier methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and blends of hydroxypropylcellulose and hydroxypropylmethylcellulose. Coat **26** optionally comprises polyethylene glycol or acetylated triglycerides. Coat **26** provides instant therapy as coat **26** dissolves or undergoes dissolution in the presence of a biological fluid and concurrently therewith delivers drug **16** to a drug receiving patient. Coat **26** provides instant therapy and it essentially overcomes the time required for the drug to be delivered from the dosage form.

Dosage form **10**, as provided by this invention, and as seen in the above drawing figures can be manufactured for administering drug **16** by the oral route, and in another embodiment, dosage form **10** comprising exterior and interior drug **16** can be sized and shaped for administering drug **16** by the sublingual and buccal routes. The sublingual and buccal routes can be used for quicker therapy and they can be used when a smaller dose of drug **16** is needed for therapy. The buccal and sublingual routes can be used as a by-pass of the first pass of hepatic metabolism of drug **16**. The sublingual or buccal routes can be used for administering the first dose of drug, followed by permitting dosage form **10** to enter the gastrointestinal tract for subsequent drug delivery.

Dosage form **10**, when manufactured as an osmotic, controlled-release dosage form, comprises at least one passageway **13**, or more than one passageway **13**. The expression "at least one passageway" includes aperture, orifice, bore, pore, porous element through which the drug can be pumped, diffuse, travel or migrate, hollow fiber, capillary tube, porous overlay, porous insert, microporous member, porous composition, and the like. The expression also includes a material that erodes or is leached from wall **12** in the fluid environment of use to produce at least one passageway in dosage form **10**. Representative material suitable for forming at least one passageway, or a multiplicity of passageways, includes an erodible poly(glycolic) acid or poly(lactic) acid member in the wall; a gelatinous filament; poly(vinyl alcohol); leachable materials such as fluid removable pore forming polysaccharides, salts, or oxides, and the like. A passageway or a plurality of passageways can be formed by leaching a material such as sorbitol, sucrose,

lactose, fructose, or the like, from the wall to provide an osmotic dimensioned pore-passageway. The passageway can have any shape such as round, triangular, square, elliptical, and the like, for assisting in the metered release of drug from dosage form **10**. Dosage form **10** can be constructed with one or passageways in spaced apart relation on one or more than a single surface of a dosage form. Passageways and equipment for forming passages are disclosed in U.S. Pat. Nos. 3,845,770 and 3,916,899 by Theeuwes and Higuchi; in U.S. Pat No. 4,063,064 by Saunders et al; and in U.S. Pat. No. 4,088,864 by Theeuwes et al. Osmotic passageways comprising controlled-drug releasing dimension, sized, shaped and adapted as a drug releasing pore formed by aqueous leaching to provide a drug-releasing pore of controlled osmotic release rate are disclosed in U.S. Pat. No. 4,200,098 by Ayer and Theeuwes; and in U.S. Pat. No. 4,285,987 by Ayer and Theeuwes.

Wall **12** of osmotic dosage form **10** can be formed in one technique using the air suspension procedure. This procedure consists in suspending and tumbling the compressed drug-push core laminate in a current of air and wall forming composition until a wall is applied to the drug-push compartment. The air suspension procedure is well-suited for independently forming the wall. The air suspension procedure is described in U.S. Pat. No. 2,799,241; *J. Am. Pharm. Assoc.,* Volume 48, pages 451 to 454, (1959); and ibid, Volume 49, pages 82 to 84, (196). Osmotic dosage forms can also be coated with a wall forming composition in a Wurster® air suspension coater, using methylene dichloride-methanol cosolvent, 80:20, wt:wt, an ethanol-water, or acetone-water cosolvent, 95:5 wt:wt using 2.5 to 4% solids. The Aeromatic® air suspension coater using a methylene dichloride-methanol cosolvent, 80:20 wt:wt, also can be used for applying the wall. Other wall forming techniques such as pan coating system, where wall forming compositions are deposited by successive spraying of the composition on the drug-push compartment, accompanied by tumbling in a rotating pan. Finally, the wall coated compartments are dried in a forced air over at 30° C. to 50° C. for up to a week to free dosage form **10** of solvent. Generally, the walls formed by these techniques have a thickness of 2 to 30 mils with a presently preferred thickness of 4 to 10 mils.

Dosage form **10** of the invention is manufactured by standard manufacturing techniques. For example, in one manufacture the beneficial drug and other ingredients comprising the drug layer facing the exit means are blended and pressed into a solid layer. The drug and other ingredients can be blended with a solvent and mixed into a solid or semisolid formed by conventional methods such a ball-milling, calendering, stirring or rollmilling and then pressed into a preselected shape. The layer possesses dimensions that correspond to the internal dimensions of the area the layer is to occupy in the dosage form and it also possesses dimensions corresponding to the second layer for forming a contacting arrangement therewith. Next, the push layer, is placed in contact with the drug layer. The push layer is manufactured using techniques for providing the drug layer. The layering of the drug layer and the push layer can be fabricated by conventional press-layering techniques. Finally, the two layer compartment forming members are surrounded and coated with an outer wall. A passageway is laser, leached, or mechanically drilled through the wall to contact the drug layer, with the dosage form optically oriented automatically by the laser equipment for forming the passageway on the preselected surface when a laser is used for forming the passageway.

In another manufacture, the dosage form is manufactured by the wet granulation technique. In the wet granulation technique, for example, the drug and the ingredients comprising the drug layer are blended using an organic solvent, such as isopropyl alcohol-ethylene dichloride 80:20 v:v (volume:volume) as the granulation fluid. Other granulating fluid such as denatured alcohol 100% can be used for this purpose. The ingredients forming the drug layer are individually passed through a 40 mesh screen and then thoroughly blended in a mixer. Next, other ingredients comprising the drug layer are dissolved in a portion of the granulation fluid, such as the cosolvent described above. Then the latter prepared wet blend is slowly added to the drug blend with continual mixing in the blender. The granulating fluid is added until a wet blend is produced, which wet mass then is forced through a 20 mesh screen onto oven trays. The blend is dried for 18 to 24 hours at 30° C. to 50° C. The dry granules are sized then with a 20 mesh screen. Next, a lubricant is passed through an 80 mesh screen and added to the dry screen granule blend. The granulation is put into milling jars and mixed on a jar mill for 1 to 15 minutes. The push layer is made by the same wet granulation techniques. The compositions are pressed into their individual layers in a Manesty® press-layer press.

Another manufacturing process that can be used for providing the compartment-forming composition layers comprises blending the powered ingredients for each layer independently in a fluid bed granulator. After the powered ingredients are dry blended in the granulator, a granulating fluid, for example, poly(vinyl-pyrrolidone) in water, or in denatured alcohol, or in 95:5 ethyl alcohol/water, or in blends of ethanol and water is sprayed onto the powders. Optionally, the ingredients can be dissolved or suspended in the granulating fluid. The coated powders are then dried in a granulator. This process granulates all the ingredients present therein while adding the granulating fluid. After the granules are dried, a lubricant such as stearic acid or magnesium stearate is added to the granulator. The granules for each separate layer are pressed then in the manner described above.

The dosage form of the invention is manufactured in another manufacture by mixing a drug with composition forming ingredients and pressing the composition into a solid lamina possessing dimensions that correspond to the internal dimensions of the compartment. In another manufacture the drug and other drug composition-forming ingredients and a solvent are mixed into a solid, or a semisolid, by conventional methods such as ballmilling, calendering, stirring or rollmilling, and then pressed into a preselected layer forming shape. Next, a layer of a composition comprising an osmopolymer and an optional osmagent are placed in contact with the layer comprising the drug. The layering of the first layer comprising the drug and the second layer comprising the osmopolymer and optional osmagent composition can be accomplished by using a conventional layer press technique. The wall can be applied by molding, spraying or dipping the pressed bilayer's shapes into wall forming materials. Another and presently preferred technique that can be used for applying the wall is the air suspension coating procedure. The procedure consists in suspending and tumbling the two layers in current of air until the wall forming composition surrounds the layers. The air suspension procedure is described in U.S. Pat. No. 2,799,241; *J. Am. Pharm. Assoc.,* Vol. 48 pp 451–454 (1979); and, ibid, Vol. 49, pp 82–84 (1960). Other standard manufacturing procedures are described in *Modern Plastics Encyclopedia,* Vol 46, pp 62–70 (1969); and in *Pharmaceu-*

tical Science, by Remington, 14th Ed., pp 1626–1678 (1970), published by Mack Publishing Co., Easton, Pa.

Exemplary solvents suitable for manufacturing the wall, the laminates and laminae include inert inorganic and organic solvents final laminated wall. The solvents broadly include members selected for the group consisting of aqueous solvents, alcohols, ketones, esters, ethers, aliphatic hydrocarbons, halogenated solvents, cyclaliphatics, aromatics, heterocyclic solvents and mixtures thereof. Typical solvents include acetone, diacetone, alcohol, methanol, ethanol, isopropyl alcohol, butyl alcohol, methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, methyl propyl ketone, n-hexane, n-heptaene ethylene glycol monoethyl ether, ethylene glycol monoethyl acetate, methylene dichloride, ethylene dichloride, propylene dichloride, carbon tetrachloride, chloroform, nitroethane, nitropropane, tetrachoroethan, ethyl ether, isopropyl ether, cyclohexane, cyclooctane, benzene, toluene, naphtha, tetrahydrofuran, diglyme, aqueous and nonaqueous mixtures thereof, such as acetone and water, acetone and methanol, acetone and ethyl alcohol, methylene dichloride and methanol, and ethylene dichloride and methanol.

DETAILED DISCLOSURE OF EXAMPLES OF THE INVENTION

The following examples are merely illustrative of the present invention and they should not be considered as limiting the scope of the invention in any way as these examples and other equivalents thereof will become apparent to those versed in the art in the light of the present disclosure, the drawings and accompanying claims.

Example 1

A dosage form adapted for delivering a drug in a therapeutic range is manufactured as follows: first a displacement or push layer is prepared by blending and passing through a stainless steel sizing screen having a mesh opening of 420 microns 587.5 grams of sodium carboxymethylcellulose having a degree of polymerization of approximately 3,200 and a degree of substitution of 0.7 carboxymethyl groups per anhydroglucose unit, 300 grams of powdered sodium chloride, 50 grams of hydroxypropylcellulose having a molecular weight of approximately 60,000 grams per mole, and 50 grams of hydroxypropylmethylcellulose having an average methoxyl content of 29 weight percent and an average hydroxypropyl content of 10 weight percent and an average molecular weight of approximately 11,300 grams per mole. Next 10 grams of red ferric oxide were passed through a sizing screen having openings of approximately 250 microns. The resulting powders were mixed in a planetary mixer to a uniform blend. The resulting blend was wet granulated by adding with stirring anhydrous ethyl alcohol until, a cohesive mass was formed. This mass was passed through a sizing screen having openings of approximately 840 microns, forming coated displacement particles, which were an dried overnight at ambient temperature and humidity. The dried particles were then passed again through the 840 micron sizing screen. Next 2.5 grams of magnesium stearate, which had been previously sized through a mesh having 180 micron openings, were tumble mixed into the coated particles.

A composition comprising a drug of the structural formula was prepared as follows: first, a drug composition was prepared by passing 840 grams of venlafaxine hydrochloride, 100 grams of hydroxypropylcellulose having a molecular weight of approximately 60,000 grams per mole, and 50 grams of polyvinylpyrrolidone having a molecular weight of approximately 40,000 grams per mole, were passed through a sizing having openings of approximately 420 microns, and mixed in a planetary mixer to yield a uniform blend. Then, anhydrous ethyl alcohol was added to the mixture with stirring to produce a cohesive damp mass. The resulting damp mass was sized through a sieve having an opening of 840 microns, producing coated venlafaxine drug, which was air dried overnight. The resulting dried coated venlafaxine drug was passed again through the sizing screen having an 840 micron opening. Next, 10 grams of magnesium stearate, sized to 180 microns, was tumble mixed into the blend.

Next, the displacement-push composition and the drug composition were formed into a bilayer core as follows: first, 87 mg of the drug composition was placed in a 9/32 inch round die cavity and lightly tamped with a standard concave round tooling to form a slightly cohesive layer. Then, 70 mg of push composition was added to die and the and the resulting fill was compressed with a final force of 2 tons, thereby forming a two layer cores.

The bilayer cores were placed next in a coating pan having a 12 inch diameter and they were coated with a wall-forming solution. The wall-forming solution was prepared by dissolving 380 grams of cellulose acetate having an acetyl content of 39.8 weight percent in 7,220 grams of acetone. In a separate mixing vessel, 20 grams of polyethylene glycol having a molecular weight of approximately 3,350 grams per mole were dissolved in approximately 380 grams of purified water. The two solutions were mixed to form the wall-coating solution which was spray coated onto the cores until about 20 mg of wall composition was deposited on the surfaces of the bilayer core.

A delivery exit port was formed across the wall by drilling an exit port, centered on the face of the dosage form on the drug composition side of the dosage form. The resulting dosage form was placed in simulated physiological fluid at 37° C., and the dosage form delivered a dose of 73 mg of venlafaxine hydrochloride at a controlled, zero rate over an extended duration of 15 hours.

Example 2

The procedure of Example 1 was followed with the manufacturing procedures as set forth, except that the drug composition comprises 890 grams of venlafaxine hydrochloride, 100 grams of hydroxypropylcellulose, and 10 grams of magnesium stearate. The resulting dosage form released in simulated intestinal fluid 77 mg of venlafaxine hydrochloride at a zero-order rate over an extended duration of 16 hours.

Example 3

The procedure of Example 1 was followed with all manufacturing steps as described, except that the drug composition consists of 650.0 grams of venlafaxine hydrochloride, 240.0 grams of maltodextrin having an average molecular weight of approximately 1800 grams per mole and an average degree of polymerization of 11.1, 80.0 grams of hydroxypropyl cellulose, 20.0 grams of polyvinyl pyrrolidone, and 10.0 grams of magnesium stearate. The resulting dosage form was tested in artificial intestinal fluid, the dosage form delivered a dose of 57 mg of venlafaxine hydrochloride at zero order rate over a period of 15 hours.

Example 4

The procedure of Example 1 was repeated with the manufacture as previously set-forth, except that the drug

composition consists of 840.0 grams of venlafaxine hydrochloride, 150.0 grams of polyethylene oxide having an average molecular weight of approximately 100,000 grams per mole, and 10.0 grams of magnesium stearate. The wall weight weighed approximately 25 mg. The resulting dosage forms were tested in simulated intestinal fluid, and they released a dose of 73 mg of venlafaxine hydrochloride at controlled rate over an extended period of 20 hours.

Example 5

The compositions were manufactured as in Example 1. The process of manufacture was the same except that the push layer manufactured was prepared in a fluid bed aqueous-based granulation process. This was accomplished by sizing the sodium carboxymethyl cellulose, the sodium chloride, the hydroxypropyl cellulose, and red ferric oxide through a screen having openings of 420 microns. The resulting powders were charged into a fluid bed granulation column and binder solution consisting of the hydroxypropyl methylcellulose at a 5 percent solids concentration in water was sprayed on, thereby forming the granules for the push layer.

Example 6

The compositions and processes followed in this example were the same as in Example 1 except the push consisted of 740.0 grams polyethylene oxide with an average molecular weight of approximately 5 million grams per mole, 200.0 grams of sodium chloride, 50.0 grams of hydroxypropyl methyl cellulose having average molecular weight of approximately 11,300 per mole, 5.0 grams of red ferric oxide, and 5.0 grams of magnesium stearate.

DESCRIPTION OF METHOD OF PERFORMING THE INVENTION

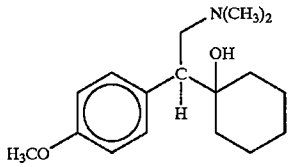
Additional embodiments of the invention pertains to a method for delivering a drug embraced by the structural formula of this invention for its intended therapy. One embodiment pertains to a method for delivering a drug of the formula by administering a dosage form comprising 0.5 mg to 750 mg of the drug from a dosage form selected from sustained-release and controlled-release dosage forms in a therapeutically responsive dose over an extended period of time. Another embodiment of the invention pertains to a method for delivering a drug of the formula disclosed in this invention, to the gastrointestinal tract of a human in need of this therapy, wherein the method comprises the steps of: (A) admitting orally into the gastrointestinal tract of the human a dosage form comprising: (1) a non-toxic wall composition comprising means for imbibing an external aqueous fluid through the wall into the dosage form, which wall surrounds and defines; (2) an internal compartment; (3) a drug composition comprising a drug of the formula in the compartment comprising a dosage unit amount of said drug; (4) a push composition in the compartment for pushing the drug composition from the compartment; (5) at least one exit means in the wall for delivering the drug from the dosage form; (B) imbibing fluid through the wall into the compartment thereby causing the composition to form a deliverable dosage form and concomitantly causing the push composition to expand and push the drug composition through the exit means from the dosage form; and (C) deliver the therapeutic drug in a therapeutically effective amount at a controlled rate over an extended period of time to the patient in need of said therapy. The method also comprising dispensing a dose amount of said drug from an instant release exterior dosage amount of drug to the patient for providing instant anti-depressant therapy.

Inasmuch as the foregoing specification comprises preferred embodiments of the invention, it is understood that variations and modifications may be made herein, in accordance with the inventive principles disclosed, without departing from the scope of the invention.

We claim:

1. A method for administering a drug to the gastrointestinal tract of a human, wherein the method comprises:

(a) admitting orally into the human a dosage form comprising a drug of the formula:



which drug possess antidepressant therapy and the dosage form comprises a member selected from the group consisting of a sustained-release dosage form and a controlled-release dosage form; and,

(b) administering the drug from the dosage form over an extended period of time in a therapeutically responsive dose to produce the antidepressant therapy.

* * * * *

Exhibit 25

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF TEXAS
LUFKIN DIVISION

ALZA CORPORATION, a Delaware corporation,

Plaintiff,

v.

WYETH, a Delaware corporation, and WYETH PHARMACEUTICALS, INC., a Delaware corporation,

Defendants.

C.A. No. 9:06cv156

JURY TRIAL DEMANDED

COMPLAINT

Plaintiff Alza Corporation ("Alza"), by its undersigned counsel, brings this action for patent infringement against defendants Wyeth and Wyeth Pharmaceuticals, Inc. (collectively "Defendants") and alleges as follows:

Jurisdiction and Venue

1. This action is based upon the Patent Laws of the United States, Title 35 of the United States Code, for infringement of United States Patent No. 6,440,457 ("the '457 Patent").

2. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

3. Venue properly lies in this judicial district under 28 U.S.C. §§ 1391 and 1400(b).

4. This Court has personal jurisdiction over Defendants.

Parties

5. Alza is a Delaware corporation with a principal place of business at 1900 Charleston Road, Mountain View, California 94039.

6. On information and belief, Wyeth is a Delaware corporation with a principal place of business at Five (5) Giraldo Farms, Madison, New Jersey 07940.

7. On information and belief, Wyeth Pharmaceuticals, Inc., is a Delaware corporation with a place of business at 500 Arcola Road, Collegeville, Pennsylvania 19426.

8. On information and belief, Wyeth Pharmaceuticals, Inc., is a subsidiary of Wyeth.

9. On information and belief, at least in part for its own benefit, Wyeth directed, authorized, assisted, cooperated with, or participated in the acts of Wyeth Pharmaceuticals, Inc., about which Alza complains.

Claim of Patent Infringement

10. Alza realleges paragraphs 1 through 9 above as if fully set forth herein.

11. On August 27, 2002, the '457 Patent, entitled "Method of Administering Antidepressant Dosage Form," was duly and legally issued by the United States Patent and Trademark Office to Alza as the assignee of the inventors, David Emil Edgren, Gurdish Kaur Bhatti, Zahedeh Hatamkhani, and Patrick S. L. Wong. The '457 Patent remains in full force and effect and will expire no earlier than August 27, 2019. A true and correct copy of the '457 Patent is attached to this Complaint as Exhibit A.

12. Alza has been and remains the owner of all right, title, and interest in and to the '457 Patent.

13. On information and belief, Defendants contributorily infringe and induce infringement of Claim 1 of the '457 Patent under 35 U.S.C. § 271, including but not limited to

§§ 271(b)-(c) and (f). Defendants contributorily infringe and induce infringement of the '457 Patent through various activities including but not limited to the manufacture, use, sale, and offer for sale of Effexor® XR products in the United States after the '457 Patent issued.

14. On information and belief, Defendants knew of the '457 Patent at all relevant times before making, using, selling, or offering for sale Effexor® XR products.

15. On information and belief, Defendants have in the past offered for sale and sold, and continue to offer for sale and sell Effexor® XR products that constitute a material part of the invention claimed in the '457 Patent and that have no substantial use other than as an infringement of the '457 Patent.

16. On information and belief, Defendants knew and intended that purchasers of Effexor® XR products would use the products in methods so as to infringe the '457 Patent.

17. On information and belief, Defendants have actively induced purchasers of Effexor® XR products to use the products in methods so as to infringe the '457 Patent.

18. On information and belief, purchasers of Effexor® XR products use the products in methods so as to infringe the '457 Patent.

19. On information and belief, Defendants have in the past willfully infringed, and continue to willfully infringe, the '457 Patent through their manufacture, use, sale, and offer for sale of Effexor® XR products.

Prayer For Relief

WHEREFORE, Alza prays for a judgment against Defendants as follows:

(a) adjudging that Defendants have infringed the '457 Patent under 35 U.S.C. § 271;

(b) ordering Defendants to account for and pay to Alza all damages caused to Alza by reason of Defendants' infringement of the '457 Patent, together with prejudgment interest on all damages;

(c) increasing the damages three times based on the willful nature of Defendants' infringement under 35 U.S.C. § 284;

(d) granting Alza its reasonable attorney fees under 35 U.S.C. § 285; and

(e) for such further and additional relief as this Court deems just and proper.

Date: July 26, 2006

By: _____

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Attorneys for Plaintiff Alza Corporation

Exhibit A

U.S. Patent No. 6,440,457

US006440457B1

(12) **United States Patent**
Edgren et al.

(10) **Patent No.: US 6,440,457 B1**
(45) **Date of Patent: Aug. 27, 2002**

(54) **METHOD OF ADMINISTERING ANTIDEPRESSANT DOSAGE FORM**

(75) Inventors: **David Emil Edgren**, El Granada; **Gurdish Kaur Bhatti**; **Zahedeh Hatamikhani**, both of Fremont; **Patrick S. L. Wong**, Palo Alto, all of CA (US)

(73) Assignee: **Alza Corporation**, Mountain View, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **08/068,480**

(22) Filed: **May 27, 1993**

(51) **Int. Cl.**[7] **A61K 9/22**; A61K 9/52; A61K 31/137; A61P 25/24

(52) **U.S. Cl.** **424/468**; 424/457; 424/473; 514/964; 514/654

(58) **Field of Search** 424/473, 468, 424/457; 514/964, 654

(56) **References Cited**

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Primary Examiner—Edward J. Webman
(74) *Attorney, Agent, or Firm*—Robert R. Neller

(57) **ABSTRACT**

The invention pertains to a dosage form **10** and to administering an antidepressant medicament **16** for an extended period of time in a rate-known dose.

1 Claim, 1 Drawing Sheet

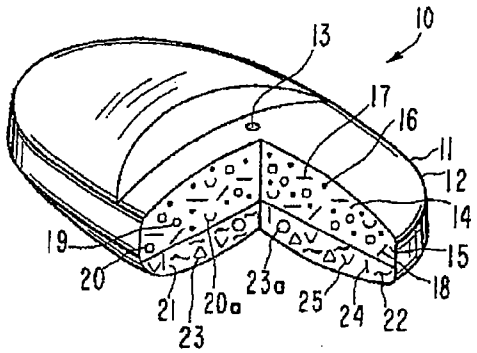


FIG. 1

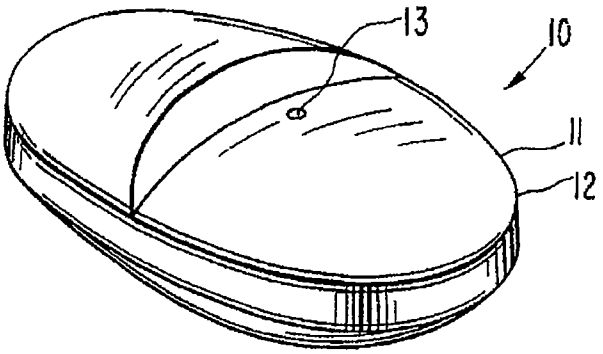


FIG. 2

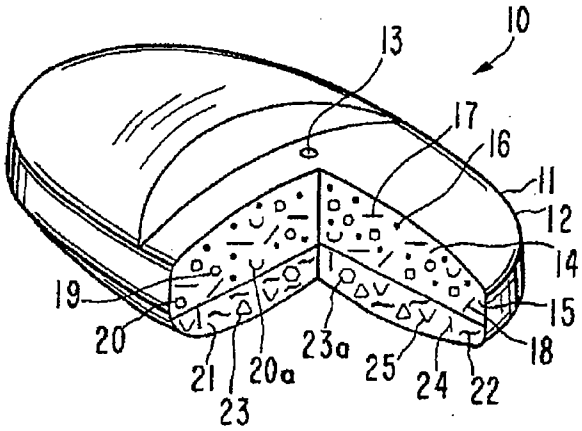
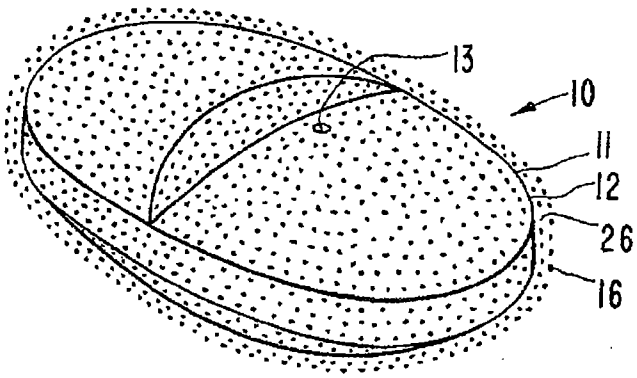


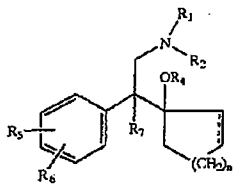
FIG. 3



METHOD OF ADMINISTERING ANTIDEPRESSANT DOSAGE FORM

FIELD OF THE INVENTION

This invention pertains to a controlled-release dosage form comprising a compound of the following structural formula:



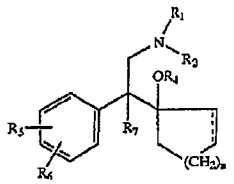
useful for antidepressant therapy. The invention concerns also a method useful for antidepressant therapy by administering the controlled-release dosage form comprising the compound of the formula.

BACKGROUND OF THE INVENTION

The primary goal of drug administration is to provide a therapeutic dose of drug in the body to achieve a desired blood concentration, and then maintain the desired drug blood concentration. The prior art, in attempts to obtain the desired therapeutic effect, often used different dosage forms or programs. One dosage program consists of a single dosing of the drug from a conventional capsule or tablet that produced a rapid rise followed by an immediate decline of the drug blood level versus time. The single dosing does not maintain the drug within a therapeutic range for an extended period of time, but exhibits of a short duration of action due to the inability of the conventional dosage form to provide drug delivery over time.

Another prior art dosing program used to obtain and to achieve drug blood levels consists in administering the drug repetitively using conventional dosage forms at various dosing intervals, as in multiple-dose therapy. In administering a drug according to the multiple-dose therapy, the drug blood level reached and the time required to reach that level depends on the dose and the dosing interval. There are, however, several potential problems inherent in multiple dose therapy. For example, if the dosing interval is not appropriate for the biological half-life of the drug, large peaks and valleys may result in the drug blood levels. Also, the drug blood level may not be within the therapeutic range at sufficiently early times, an important consideration for many disease states. And too, patient noncompliance with the multiple dosing regimen can result in a failure of this approach, especially as a drug in circulation surges to a high each time the drug is administered followed by a decline in drug concentration in the blood and in body compartments. Thus, a graph of drug in circulation following a dosage program of several doses, has an appearance of a series of peaks:, which may surpass the toxic threshold. Then, each time the blood levels decreases into valleys, below a critical level needed to achieve a desired therapeutic effect, that effect may not be obtainable in the blood and body. Conventional dosage forms and their mode of operation are discussed in *Remington's Pharmaceutical Sciences*, 18th Edition, pages 1676 to 1686, (1990), Mack Publishing Co.; *The Pharmacological Basis of Therapeutics*, 7th Edition, page 7 (1985) published by MacMillian Publishing Co., and in U.S. Pat. Nos. 3,598,122 and 3,598,123 both issued to Zaffaroni.

A critical need exists for a controlled-rate dosage form for administering the drug of the formula:



which drug is presently administered in conventional dosage forms including tablets, capsules, elixirs and suspensions. These conventional dosage forms produce the peaks and valleys drug pattern presented above and they do not provide for controlled-rate therapy over an extended period of time. The drug of the formula is dosed twice or thrice a day now because of its elimination half-life of three to five hours. This pattern of dosing indicates the need for a controlled-release dosage form that can administer the drug at a controlled rate over an extended time to provide constant therapy and thereby eliminate the need for multiple dosing. The drugs of the structural formula are known in U.S. Pat. Nos. 4,535,186; 4,611,078; and 4,761,501 all issued to Husbands, Yardley and Muth.

The prior art provided controlled-release dosage forms that can continuously over time administer a drug for controlled-rate therapy. For example, in U.S. Pat. No. 4,327,725 issued to Cortese and Theeuwes and in U.S. Pat. Nos. 4,612,008; 4,765,989; and 4,783,337 issued to Wong, Barclay, Deters, and Theeuwes. The dosage forms disclosed in these patents provide a drug at a constant rate for effecting a therapeutic range for preferred therapy. The dosage forms of the patents provide a therapeutic range and avoids delivering the drug in excess in a toxic range with its accompanying side-effects. The dosage forms of the patents in providing a controlled dose in a therapeutic range also avoids delivering the drug in an ineffective dose in an ineffective range.

The dosage forms presented immediately above operate successfully for their intended use and they can deliver many drugs indicated for good therapy. The drugs of the above structural formula, however, possess properties such as a high solubility of 570 mg per ml at a body temperature of 37° C. that can lead to a premature release of the drug from the dosage form. During operation of the dosage forms, the convection motion of the imbibed fluid, and the hydrostatic pressure of the imbibed fluid coupled with the high solubility can result in the premature release of the drugs of the formula.

It is immediately apparent in the light of the above presentation that an urgent need exists for a dosage form endowed with controlled-release delivery for delivering the drugs embraced by the structural formula. The need exists for the dosage form for delivering the drug at a controlled dose in a therapeutic range while simultaneously providing the intended therapy. It will be appreciated by those versed in the dispensing art, that such a dosage form that can administer the drug in a controlled-rate dose over time, would, represent an advancement and a valuable contribution to the art.

OBJECTS OF THE INVENTION

Accordingly, in view of the above presentation, it is an immediate object of this invention to provide a dosage from

that possesses controlled-release delivery for providing a dosage form for administering a drug of the structural formula.

Another object of the present invention is to provide a dosage form for administering the drug of the formula in a controlled-rate dose in a therapeutic range over a prolonged period of time.

Another object of the present invention is to provide a dosage form that can deliver the drug of the formula essentially-free of a premature release from the dosage form.

Another object of the present invention is to provide a drug delivery controlled-release system that can deliver a drug for maintaining constant drug levels in the blood thereby functioning as a prolonged release system.

Another object of the present invention is to provide drug delivery sustained-release system that provides slow release of the drug over an extended period of time optionally in a therapeutic range.

Another object of the present invention is to provide a dosage form that substantially reduces and/or substantially eliminates the unwanted influences of a gastrointestinal environment of use and still provides controlled drug administration.

Another object of the present invention is to provide an improvement in a dosage form for administering a drug embraced by the structural formula and its pharmaceutically acceptable salt, wherein the improvement comprises delivering the drug in a controlled-release rate from the dosage form for improved and known therapy.

Another object of the invention is to provide a once-a-day controlled-release dosage form to deliver the drug of the structural formula orally to a patent in need of therapy.

Another object of the invention is to provide a method for administering a drug of the formula by orally administering the drug in a controlled rate dose per unit dose over an extended time to an animal in need of therapy.

Another object of the present invention is to provide a method for administering a drug of the formula in a therapeutic range while simultaneously substantially-avoiding a toxic range and an infective range.

Another object of the present invention is to provide a therapeutic composition comprising a drug of the structural formula blended with a drug-composition forming polymer.

Another object of the invention is to provide a therapeutic composition comprising a member selected from the group consisting of venlafaxine and its pharmaceutically acceptable additional salt and a pharmaceutically acceptable polymer carrier for venlafaxine and its acceptable salts.

Other objects, feature, and advantages of the invention will more apparent to those versed in the dispensing arts from the following detailed specification, taken in conjunction with the drawings and the accompanying claims.

BRIEF DESCRIPTION OF THE DRAWINGS

In the drawing figures, which are not drawn to scale, but are set forth to illustrate various embodiments of the invention, the drawing figures are as follows:

Drawing FIG. 1 is a general view of a dosage form provided by the invention, which dosage form is designed and shaped for oral administration, and for a drug delivery in a controlled-rate dose in the gastrointestinal tract;

Drawing FIG. 2 is an opened view of the dosage form of drawing FIG. 1 for depicting the structure of the dosage form and the composition member contained inside the dosage form; and

Drawing FIG. 3 is a view of a dosage form that depicts an external, instant-release of drug of the structural formula coated on the exterior surface of the dosage form.

In the drawing figures, and in the specification, like parts in related figures are identified by like numbers. The terms appearing earlier in the specification and in the description of the drawing figures, as well as embodiments thereof, are further described elsewhere in the disclosure.

DETAILED DESCRIPTION OF THE DRAWINGS

Turning now to the drawing figures in detail, which drawing figures are examples of dosage forms provided by this invention, and which examples are not to be construed as limiting, one example of a dosage form is seen in drawing FIG. 1. In drawing FIG. 1, a dosage form **10** is seen comprising a body member **11**, which body **11** comprises wall **12**, that surrounds and forms an internal area, not seen in drawing FIG. 1. Dosage form **10** comprises at least one exit port **13** for connecting the exterior with the interior of dosage form **10**.

The dosage form **10** of drawing FIG. 1 illustrates a controlled-release dosage form manufactured as an osmotic dosage form that delivers a drug by osmotic action over an extended period of time. The dosage form comprising controlled-release properties embraced by this invention are successful at maintaining substantially constant drug levels in the blood or in a tissue. The dosage forms within the mode and manner of this invention comprises also sustained-release dosage forms. The sustained-release dosage forms releases the drug and provide drug levels in the blood or target tissue within a therapeutic range over an extended period of time. The invention embraces additionally prolonged release dosage forms. The prolonged release dosage form denotes extended duration of drug delivery action over that achieved by conventional drug delivery.

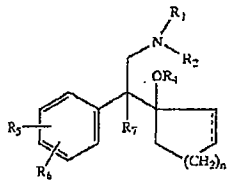
In drawing FIG. 2, dosage form **10** of FIG. 1 is seen in opened section. In drawing FIG. 2, dosage form **10** comprises a body **11**, a wall **12** that surrounds and defines an internal compartment **14**. In drawing FIG. 2, internal compartment **14** communicates through an exit passageway **13** with the exterior of dosage form **10**.

Wall **12** of dosage form **10** comprises totally or in at least a part of a composition that is permeable to the passage of an exterior fluid present in an environment of use, such as aqueous and biological fluids. Wall **12** is formed of nontoxic ingredients, is substantially impermeable to the passage of a drug and other ingredients present in compartment **14**. Wall **12** comprises a composition that is substantially inert, that is, wall **12** maintains its physical and chemical integrity during the drug dispensing life of a drug from dosage form **10**. The phrase, "maintaining its physical and chemical integrity," means wall **12** does not lose its structure and it does not change during the dispensing life of dosage form **10**, except for possible leaching of one or more exit **13** passageway formed during operation of dosage form **10** or for leaching a water-soluble flux enhancers blended into wall **12**. Wall **12** comprises a material that does not adversely affect an animal, a human or any other components comprising the dosage form. Representative materials for forming wall **12**, are in one embodiment, a cellulose ester polymer, a cellulose ether polymer and a cellulose esterether polymer. These cellulosic polymers have a degree of substitution. D.S., on the anhydroglucose unit, from greater than 0 up to 3 inclusive. By degree of substitution is meant the average number of hydroxyl groups originally present on the anhydroglucose unit comprising the cellulose polymer that are replaced by a

substituting group. Representative materials include a member selected from the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, mono-, di- and tricellulose alkanylates, mono-, di-, and tricellulose aroylates, and the like. Exemplary polymers include cellulose acetate having a D.S. up to 1 and an acetyl content up to 21%; cellulose acetate having a D.S. of 1 to 2 and an acetyl content of 21 to 35 %; cellulose acetate having a D.S. of 2 to 3 and an acetyl content of 35 to 44.8%, and the like. More specific cellulosic polymers include cellulose propionate having a D.S. of 1.8 and a propyl content of 39.2 to 45% and a hydroxyl content of 2.8 to 5.4%; cellulose acetate butyrate having a D.S. of 1.8, an acetyl content of 13 to 15% and a butyryl content of 34 to 39%; cellulose acetate butyrate having an acetyl content of 2 to 29%, a butyryl content of 17 to 53% and a hydroxyl content of 0.5 to 4.7; cellulose triacylates having a D.S. of 2.9 to 3 such as cellulose trivalerate, cellulose trilaurate, cellulose tripalmitate, cellulose trisuccinate, and cellulose trioctanoate; cellulose diacylates having a D.S. of 2.2 to 2.6 such as cellulose disuccinate, cellulose dipalmitate, cellulose dioctanoate, cellulose dipentanoate, co-esters of cellulose such as cellulose acetate butyrate and cellulose acetate propionate, and the like.

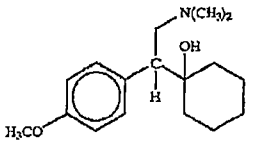
Additional polymers include ethyl cellulose of various degree of etherification with ethoxy content of from 40% to 55%, acetaldehyde dimethyl cellulose acetate, cellulose acetate ethyl carbamate, cellulose acetate methyl carbamate, cellulose acetate diethyl aminoacetate, semipermeable polyamides; semipermeable polyurethanes; semipermeable sulfonated polystyrenes; semipermeable cross-linked selective polymers formed by the coprecipitation of a polyanion and a polycation as disclosed in U.S. Pat Nos. 3,173,876, 3,276,586, 3,541,005; 3,541,006, and 3,546,142; semipermeable polymers as disclosed by Loeb and Sourirajan in U.S. Pat. No. 3,133,132; semipermeable lightly cross-linked polystyrene derivatives, semipermeable cross-linked poly (sodium styrene sulfonate); semipermeable cross-linked poly(vinylbenzyltrimethyl ammonium chloride); semipermeable polymers exhibiting a fluid permeability of 2.5×10^{-8} to 2.5×10^{-4} (cm^2/hr.atm) expressed per atmosphere of hydrostatic or osmotic pressure difference across the semipermeable wall. The polymers are known to the art in U.S. Pat. Nos. 3,845,770; 3,916,899; and 4,160,020; and in *Handbook of Common Polymers* by Scott, J. R. and Roff, W. J., 1971 published by CRC Press, Cleveland, Ohio.

Compartment 14 comprises a drug composition, identified as drug layer 15 which contains drug 16, identified by dots. Drug 16 comprises a drug of the following structural formula:



wherein the dotted line represents optional unsaturation or a cycloalkenyl moiety; R_1 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbon atoms; R_2 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbon atoms; R_4 is a member selected from the group consisting of hydrogen, alkyl of 1 to 6 carbon atoms, formyl, and alkanoyl of 2 to 7 carbon atoms; R_5 and R_6 are independently a member selected from the group consisting of hydrogen, hydroxyl, an alkyd of 1 to 6 carbon atoms, an alkoxy of 1 to 6 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, nitro, alkylmercapto of 1 to 6 carbon atoms, amino, alkylamino of 1 to 6 carbon atoms in which each alkyl group comprises 1 to 6 carbon atoms, alkanamido of 2 to 7 carbon atoms, halo, and trifluoroethyl, R_7 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbons, and n is one of the integers 0, 1, 2, 3, and 4. The formula embraces also the pharmaceutically acceptable addition salts including a member selected from the group consisting of inorganic, organic, hydrochloric, hydrobromic, gluconic, fumaric, maleric, sulfonic, succinic, sulfuric, phosphoric, tartaric, acetic, proponic, citric, oxalic and similar pharmaceutically acceptable addition salts. The compounds are known in U.S. Pat. Nos. 4,535,186; 4,611,078; 4,761,501; and 5,190,765.

The drugs of the structural formula are represented by the drug 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol of the structural formula:



The drug embraced by the formula possesses antidepressant properties. The drug in vitro prevents the neuronal uptake of serotonin, norepinephrine, and dopamine and it does not inhibit monoamine oxidase. The drug antagonizes reserpine-induced hypothermia and potentiates the effects of levodopa, and reduces histamine-induced corticotropin release and induces cyclicadenosine monophosphate subsensitivity after both acute and chronic administration. The drug possesses excellent antidepressant activity in humans. The therapeutic amount of drug 16 in dosage form 10 is 0.5 mg to 750 mg, with individual dosage forms comprising 2, 5, 10, 25, 40, 50, 75, 100, 150, 250, 300, 500, and 600 mg of drug 16 for administering in a single dose or in more then one dose over an extended period of 24 hours. The therapeutic properties of the drug embraced by the structural formula are reported in *Current Therapeutic Research*, Vol. 42, No. 5, pages 901 to 909 (1987).

Composition 15 comprising drug 16 may comprise a drug dispensing carrier and composition formulating member consisting of a member selected from the group consisting of 0 wt % to 25 wt % of a hydroxypropylalkylcellulose where alkyl consists of 1 to 7 carbons selected from the group consisting of methyl, ethyl, isopropyl, butyl, pentyl, and hexyl which cellulose member comprises a 9,000 to 1,250,000 molecular weight and is exemplified by hydroxypropylmethylcellulose, hydroxypropylethylcellulose, hydroxypropylisopropylcellulose, hydroxypropylbutylcellulose and hydroxypropylhexylcellulose represented by dashes 17; a member selected from the group consisting of 0 wt % to 20 wt % hydroxylalkylcellulose where alkyl is 1 to 6 carbons including methyl, ethyl, propyl, butyl, pentyl, and hexyl which cellulose member comprises a 7,500 to 750,000 molecular weight and is exemplified by hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxyisopropylcellulose and

hydroxybutylcellulose as represented by slanted line 18; a member selected from the group consisting of 0 wt % to 35 wt % of a vinyl-polymer having a 3,500 to 750,000 molecular weight represented by poly-n-vinylamide, poly-n-vinylacetamide, poly-n-vinylethylacetamide, poly-n-vinylmethylpropionamide, poly-n-vinyl ethylpropionamide, poly-n-vinylmethylisobutyramide, poly-n-vinyl-2-pyrrolidone, poly-n-vinypiperidone also known as polyvinylpyrrolidone and as poly-n-vinylpyrroledone, poly-n-vinylcaprolactam, poly-n-vinyl-5-methyl-2-pyrrolidone and poly-n-vinyl-3-methyl-2-pyrrolidone, and poly-n-vinylpyrrolidone copolymer with a member selected from the group consisting of vinyl acetate, vinyl alcohol, vinyl chloride, vinyl fluoride, vinyl butyrate, vinyl laurate and vinyl stearate represented by small circles 19; and 0 wt %, where wt % is weight percent, 35 wt % of a maltodextrin polymer composition comprising the formula $(C_6H_{12}O_5)_n H_2O$ wherein n is 3 to 7,500 and the maltodextrin polymer comprises a 500 to 1,250,000 number average molecular weight represented by a small square 20; as member selected from the group consisting of 0 wt % to 40 wt % of poly(etheylen oxide) having a molecular weight of 100,000 to 600,000 grams per mole, represented by half-circles 20*a*. Composition 15 optionally comprises from 0 to 4.5 wt % of a lubricant represented by magnesium stearate, calcium stearate or stearic acid. The total weight of all ingredients in composition 15 is equal to 100 wt %, weight percent.

Compartment 14 comprises a displacement composition or push layer 21. Displacement composition 21 comprises a polymer member selected from the group consisting of a polymer possessing a repeating molecular unit $-(O-CH_2CH_2)_n-$ wherein n is a positive whole number of 50,000 to 300,000 as represented by a poly(alkylene oxide) comprising poly(ethylene oxide) seen as wavy line 22; a maltodextrin polymer of the formula $(C_6H_{12}O_5)_n H_2O$ wherein n is 50 to 62,000 and comprises a 9,000 to 10,000,000 molecular weight and represented by triangle 23; a carboxymethylcellulose polymer comprising a 10,000 to 5,000,000 molecular weight represented by alkali carboxymethylcellulose, sodium carboxymethylcellulose and potassium carboxymethylcellulose, ammonium carboxymethylcellulose, sodium carboxymethyl-2-hydroxyethylcellulose, sodium carboxymethylmethylcellulose, alkali carboxymethyl-hydroxypropylmethylcellulose, alkali carboxymethyl-2-hydroxyethylmethylcellulose, alkali carboxymethyl-2-hydroxybutylmethylcellulose, alkali carboxymethyl-2-hydroxyethyl-ethylcellulose and alkali carboxymethyl-2-hydroxypropylcellulose, where alkali is sodium and potassium and seen in drawing FIG. 2 as hexagonal 23*a*. The polymers in push layer 21 provide unforeseen operating advantages as the polymer maintains its chemical composition during operation as it imbibes an external aqueous fluid including biological fluid while simultaneously pushing the drug from the dosage form essentially-free of substantially mixing the drug composition with the push composition. The displacement composition 21 comprises optionally from 4 to 35 wt % of an osmotically active compound, also known as osmagent and represented by vertical line 24. Representative of osmotically effective compounds comprises salts, oxides, esters that exhibit imbibition properties, carbohydrates and acids including a member selected from the group consisting of magnesium sulfate, magnesium chloride, sodium chloride, lithium chloride, potassium chloride, potassium sulfate, sodium sulfate, sodium sulfite, lithium sulfate, ammonium chloride, potassium lactate, mannitol, urea,: magnesium succinate, tartaric acid, raffinose, sorbitol, sucrose, fructose, and glucose. Displacement layer 21 optionally comprises 0.5 wt % to 30 wt % of a cellulose polymer 25 represented by the letter v. Representative of cellulose polymer 25 comprise a member selected from the group consisting of hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxypropylethylcellulose, hydroxypropylisopropylcellulose, hydroxypropylbutylcellulose, hydroxypropylpentylcellulose, and hydroxypropylhexylcellulose comprising a 9,000 to 225,000 molecular weight. The displacement composition optionally comprises 0 wt % to 5 wt % of lubricant stearic acid and, magnesium stearate, calcium oleate, oleic acid, and caprylic acid. The polymers are known in U.S. Pat Nos. 3,845,770; and 4,160,020; in *Handbook of Common Polymers* by Scott, J. R., and Roff, W. J., published by CRC Press, Cleveland, Ohio.

Dosage form 10, a seen in drawing FIG. 3 depicts another preferred manufacture provided by the invention. Dosage form 10, in drawing FIG. 3, comprises an external coat on a the exterior surface of dosage form 10. Coat 26 is a therapeutic composition comprising 10 mg to 150 mg of drug 16, represented by dots 16. Exterior coat 26 provides instant drug 16 for instant therapy. Drug 16 is blended with an aqueous-soluble composition comprising a carrier methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and blends of hydroxypropylcellulose and hydroxypropylmethylcellulose. Coat 26 optionally comprises polyethylene glycol or acetylated triglycerides. Coat 26 provides instant therapy as coat 26 dissolves or undergoes dissolution in the presence of a biological fluid and concurrently therewith delivers drug 16 to a drug receiving patient. Coat 26 provides instant therapy and it essentially overcomes the time required for the drug to be delivered from the dosage form.

Dosage form 10, as provided by this invention, and as seen in the above drawing figures can be manufactured for administering drug 16 by the oral route, and in another embodiment, dosage form 10 comprising exterior and interior drug 16 can be sized and shaped for administering drug 16 by the sublingual and buccal routes. The sublingual and buccal routes can be used for quicker therapy and they can be used when a smaller dose of drug 16 is needed for therapy. The buccal and sublingual routes can be used as a by-pass of the first pass of hepatic metabolism of drug 16. The sublingual or buccal routes can be used for administering the first dose of drug, followed by permitting dosage form 10 to enter the gastrointestinal tract for subsequent drug delivery.

Dosage form 10, when manufactured as an osmotic, controlled-release dosage form, comprises at least one passageway 13, or more than one passageway 13. The expression "at least one passageway" includes aperture, orifice, bore, pore, porous element through which the drug can be pumped, diffuse, travel or migrate, hollow fiber, capillary tube, porous overlay, porous insert, microporous member, porous composition, and the like. The expression also includes a material that erodes or is leached from wall 12 in the fluid environment of use to produce at least one passageway in dosage form 10. Representative material suitable for forming at least one passageway, or a multiplicity of passageways, includes an erodible poly(glycolic) acid or poly(lactic) acid member in the wall; a gelatinous filament; poly(vinyl alcohol); leachable materials such as fluid removable pore forming polysaccharides, salts, or oxides, and the like. A passageway or a plurality of passageways can be formed by leaching a material such as sorbitol, sucrose,

lactose, fructose, or the like, from the wall to provide an osmotic dimensioned pore-passageway. The passageway can have any shape such as round, triangular, square, elliptical, and the like, for assisting in the metered release of drug from dosage form 10. Dosage form 10 can be constructed with one or passageways in spaced apart relation on one or more than a single surface of a dosage form. Passageways and equipment for forming passages are disclosed in U.S. Pat. Nos. 3,845,770 and 3,916,899 by Theeuwes and Higuchi; in U.S. Pat No. 4,063,064 by Saunders et al; and in U.S. Pat. No. 4,088,864 by Theeuwes et al. Osmotic passageways comprising controlled-drug releasing dimension, sized, shaped and adapted as a drug releasing pore formed by aqueous leaching to provide a drug-releasing pore of controlled osmotic release rate are disclosed in U.S. Pat. No. 4,200,098 by Ayer and Theeuwes; and in U.S. Pat. No. 4,285,987 by Ayer and Theeuwes.

Wall 12 of osmotic dosage form 10 can be formed in one technique using the air suspension procedure. This procedure consists in suspending and tumbling the compressed drug-push core laminate in a current of air and wall forming composition until a wall is applied to the drug-push compartment. The air suspension procedure is well-suited for independently forming the wall. The air suspension procedure is described in U.S. Pat. No. 2,799,241; *J. Am. Pharm. Assoc.*, Volume 48, pages 451 to 454, (1959); and ibid, Volume 49, pages 82 to 84, (196). Osmotic dosage forms can also be coated with a wall forming composition in a Wurster® air suspension coater, using methylene dichloride-methanol cosolvent, 80:20, wt:wt, an ethanol-water, or acetone-water cosolvent, 95:5 wt:wt using 2.5 to 4% solids. The Aeromatic® air suspension coater using a methylene dichloride-methanol cosolvent, 80:20 wt:wt, also can be used for applying the wall. Other wall forming techniques such as pan coating system, where wall forming compositions are deposited by successive spraying of the composition on the drug-push compartment, accompanied by tumbling in a rotating pan. Finally, the wall coated compartments are dried in a forced air over at 30° C. to 50° C. for up to a week to free dosage form 10 of solvent. Generally, the walls formed by these techniques have a thickness of 2 to 30 mils with a presently preferred thickness of 4 to 10 mils.

Dosage form 10 of the invention is manufactured by standard manufacturing techniques. For example, in one manufacture the beneficial drug and other ingredients comprising the drug layer facing the exit means are blended and pressed into a solid layer. The drug and other ingredients can be blended with a solvent and mixed into a solid or semisolid formed by conventional methods such a ball-milling, calendering, stirring or rollmilling and then pressed into a preselected shape. The layer possesses dimensions that correspond to the internal dimensions of the area the layer is to occupy in the dosage form and it also possesses dimensions corresponding to the second layer for forming a contacting arrangement therewith. Next, the push layer, is placed in contact with the drug layer. The push layer is manufactured using techniques for providing the drug layer. The layering of the drug layer and the push layer can be fabricated by conventional press-layering techniques. Finally, the two layer compartment forming members are surrounded and coated with an outer wall. A passageway is laser, leached, or mechanically drilled through the wall to contact the drug layer, with the dosage form optically oriented automatically by the laser equipment for forming the passageway on the preselected surface when a laser is used for forming the passageway.

In another manufacture, the dosage form is manufactured by the wet granulation technique. In the wet granulation technique, for example, the drug and the ingredients comprising the drug layer are blended using an organic solvent, such as isopropyl alcohol-ethylene dichloride 80:20 v:v (volume:volume) as the granulation fluid. Other granulating fluid such as denatured alcohol 100% can be used for this purpose. The ingredients forming the drug layer are individually passed through a 40 mesh screen and then thoroughly blended in a mixer. Next, other ingredients comprising the drug layer are dissolved in a portion of the granulation fluid, such as the cosolvent described above. Then the latter prepared wet blend is slowly added to the drug blend with continual mixing in the blender. The granulating fluid is added until a wet blend is produced, which wet mass then is forced through a 20 mesh screen onto oven trays. The blend is dried for 18 to 24 hours at 30° C. to 50° C. The dry granules are sized then with a 20 mesh screen. Next, a lubricant is passed through an 80 mesh screen and added to the dry screen granule blend. The granulation is put into milling jars and mixed on a jar mill for 1 to 15 minutes. The push layer is made by the same wet granulation techniques. The compositions are pressed into their individual layers in a Manesty® press-layer press.

Another manufacturing process that can be used for providing the compartment-forming composition layers comprises blending the powered ingredients for each layer independently in a fluid bed granulator. After the powered ingredients are dry blended in the granulator, a granulating fluid, for example, poly(vinyl-pyrrolidone) in water, or in denatured alcohol, or in 95:5 ethyl alcohol/water, or in blends of ethanol and water is sprayed onto the powders. Optionally, the ingredients can be dissolved or suspended in the granulating fluid. The coated powders are then dried in a granulator. This process granulates all the ingredients present therein while adding the granulating fluid. After the granules are dried, a lubricant such as stearic acid or magnesium stearate is added to the granulator. The granules for each separate layer are pressed then in the manner described above.

The dosage form of the invention is manufactured in another manufacture by mixing a drug with composition forming ingredients and pressing the composition into a solid lamina possessing dimensions that correspond to the internal dimensions of the compartment. In another manufacture the drug and other drug composition-forming ingredients and a solvent are mixed into a solid, or a semisolid, by conventional methods such as ballmilling, calendering, stirring or rollmilling, and then pressed into a preselected layer forming shape. Next, a layer of a composition comprising an osmopolymer and an optional osmagent are placed in contact with the layer comprising the drug. The layering of the first layer comprising the drug and the second layer comprising the osmopolymer and optional osmagent composition can be accomplished by using a conventional layer press technique. The wall can be applied by molding, spraying or dipping the pressed bilayer's shapes into wall forming materials. Another and presently preferred technique that can be used for applying the wall is the air suspension coating procedure. The procedure consists in suspending and tumbling the two layers in current of air until the wall forming composition surrounds the layers. The air suspension procedure is described in U.S. Pat. No. 2,799,241; *J. Am. Pharm. Assoc.*, Vol. 48 pp 451–454 (1979); and, ibid, Vol. 49, pp 82–84 (1960). Other standard manufacturing procedures are described in *Modern Plastics Encyclopedia*, Vol 46, pp 62–70 (1969); and in *Pharmaceu-*

tical Science, by Remington, 14th Ed., pp 1626–1678 (1970), published by Mack Publishing Co., Easton, Pa.

Exemplary solvents suitable for manufacturing the wall, the laminates and laminae include inert inorganic and organic solvents final laminated wall. The solvents broadly include members selected for the group consisting of aqueous solvents, alcohols, ketones, esters, ethers, aliphatic hydrocarbons, halogenated solvents, cyclaliphatics, aromatics, heterocyclic solvents and mixtures thereof. Typical solvents include acetone, diacetone, alcohol, methanol, ethanol, isopropyl alcohol, butyl alcohol, methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, methyl propyl ketone, n-hexane, n-heptaene ethylene glycol monoethyl ether, ethylene glycol monoethyl acetate, methylene dichloride, ethylene dichloride, propylene dichloride, carbon tetrachloride, chloroform, nitroethane, nitropropane, tetrachoroethan, ethyl ether, isopropyl ether, cyclohexane, cyclooctane, benzene, toluene, naphtha, tetrahydrofuran, diglyme, aqueous and nonaqueous mixtures thereof, such as acetone and water, acetone and methanol, acetone and ethyl alcohol, methylene dichloride and methanol, and ethylene dichloride and methanol.

DETAILED DISCLOSURE OF EXAMPLES OF THE INVENTION

The following examples are merely illustrative of the present invention and they should not be considered as limiting the scope of the invention in any way as these examples and other equivalents thereof will become apparent to those versed in the art in the light of the present disclosure, the drawings and accompanying claims.

Example 1

A dosage form adapted for delivering a drug in a therapeutic range is manufactured as follows: first a displacement or push layer is prepared by blending and passing through a stainless steel sizing screen having a mesh opening of 420 microns 587.5 grams of sodium carboxymethylcellulose having a degree of polymerization of approximately 3,200 and a degree of substitution of 0.7 carboxymethyl groups per anhydroglucose unit, 300 grams of powdered sodium chloride, 50 grams of hydroxypropylcellulose having a molecular weight of approximately 60,000 grams per mole, and 50 grams of hydroxypropylmethylcellulose having an average methoxyl content of 29 weight percent and an average hydroxypropyl content of 10 weight percent and an average molecular weight of approximately 11,300 grams per mole. Next 10 grams of red ferric oxide were passed through a sizing screen having openings of approximately 250 microns. The resulting powders were mixed in a planetary mixer to a uniform blend. The resulting blend was wet granulated by adding with stirring anhydrous ethyl alcohol until, a cohesive mass was formed. This mass was passed through a sizing screen having openings of approximately 840 microns, forming coated displacement particles, which were an dried overnight at ambient temperature and humidity. The dried particles were then passed again through the 840 micron sizing screen. Next 2.5 grams of magnesium stearate, which had been previously sized through a mesh having 180 micron openings, were tumble mixed into the coated particles.

A composition comprising a drug of the structural formula was prepared as follows: first, a drug composition was prepared by passing 840 grams of venlafaxine hydrochloride, 100 grams of hydroxypropylcellulose having a molecular weight of approximately 60,000 grams per mole, and 50 grams of polyvinylpyrrolidone having a molecular weight of approximately 40,000 grams per mole, were passed through a sizing having openings of approximately 420 microns, and mixed in a planetary mixer to yield a uniform blend. Then, anhydrous ethyl alcohol was added to the mixture with stirring to produce a cohesive damp mass. The resulting damp mass was sized through a sieve having an opening of 840 microns, producing coated venlafaxine drug, which was air dried overnight. The resulting dried coated venlafaxine drug was passed again through the sizing screen having an 840 micron opening. Next, 10 grams of magnesium stearate, sized to 180 microns, was tumble mixed into the blend.

Next, the displacement-push composition and the drug composition were formed into a bilayer core as follows: first, 87 mg of the drug composition was placed in a 9/32 inch round die cavity and lightly tamped with a standard concave round tooling to form a slightly cohesive layer. Then, 70 mg of push composition was added to die and the and the resulting fill was compressed with a final force of 2 tons, thereby forming a two layer cores.

The bilayer cores were placed next in a coating pan having a 12 inch diameter and they were coated with a wall-forming solution. The wall-forming solution was prepared by dissolving 380 grams of cellulose acetate having an acetyl content of 39.8 weight percent in 7,220 grams of acetone. In a separate mixing vessel, 20 grams of polyethylene glycol having a molecular weight of approximately 3,350 grams per mole were dissolved in approximately 380 grams of purified water. The two solutions were mixed to form the wall-coating solution which was spray coated onto the cores until about 20 mg of wall composition was deposited on the surfaces of the bilayer core.

A delivery exit port was formed across the wall by drilling an exit port, centered on the face of the dosage form on the drug composition side of the dosage form. The resulting dosage form was placed in simulated physiological fluid at 37° C., and the dosage form delivered a dose of 73 mg of venlafaxine hydrochloride at a controlled, zero rate over an extended duration of 15 hours.

Example 2

The procedure of Example 1 was followed with the manufacturing procedures as set forth, except that the drug composition comprises 890 grams of venlafaxine hydrochloride, 100 grams of hydroxypropylcellulose, and 10 grams of magnesium stearate. The resulting dosage form released in simulated intestinal fluid 77 mg of venlafaxine hydrochloride at a zero-order rate over an extended duration of 16 hours.

Example 3

The procedure of Example 1 was followed with all manufacturing steps as described, except that the drug composition consists of 650.0 grams of venlafaxine hydrochloride, 240.0 grams of maltodextrin having an average molecular weight of approximately 1800 grams per mole and an average degree of polymerization of 11.1, 80.0 grams of hydroxypropyl cellulose, 20.0 grams of polyvinyl pyrrolidone, and 10.0 grams of magnesium stearate. The resulting dosage form was tested in artificial intestinal fluid, the dosage form delivered a dose of 57 mg of venlafaxine hydrochloride at zero order rate over a period of 15 hours.

Example 4

The procedure of Example 1 was repeated with the manufacture as previously set-forth, except that the drug

composition consists of 840.0 grams of venlafaxine hydrochloride, 150.0 grams of polyethylene oxide having an average molecular weight of approximately 100,000 grams per mole, and 10.0 grams of magnesium stearate. The wall weight weighed approximately 25 mg. The resulting dosage forms were tested in simulated intestinal fluid, and they released a dose of 73 mg of venlafaxine hydrochloride at controlled rate over an extended period of 20 hours.

Example 5

The compositions were manufactured as in Example 1. The process of manufacture was the same except that the push layer manufactured was prepared in a fluid bed aqueous-based granulation process. This was accomplished by sizing the sodium carboxymethyl cellulose, the sodium chloride, the hydroxypropyl cellulose, and red ferric oxide through a screen having openings of 420 microns. The resulting powders were charged into a fluid bed granulation column and binder solution consisting of the hydroxypropyl methylcellulose at a 5 percent solids concentration in water was sprayed on, thereby forming the granules for the push layer.

Example 6

The compositions and processes followed in this example were the same as in Example 1 except the push consisted of 740.0 grams polyethylene oxide with an average molecular weight of approximately 5 million grams per mole, 200.0 grams of sodium chloride, 50.0 grams of hydroxypropyl methyl cellulose having average molecular weight of approximately 11,300 per mole, 5.0 grams of red ferric oxide, and 5.0 grams of magnesium stearate.

DESCRIPTION OF METHOD OF PERFORMING THE INVENTION

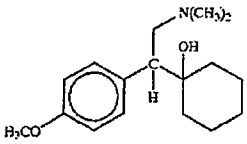
Additional embodiments of the invention pertains to a method for delivering a drug embraced by the structural formula of this invention for its intended therapy. One embodiment pertains to a method for delivering a drug of the formula by administering a dosage form comprising 0.5 mg to 750 mg of the drug from a dosage form selected from sustained-release and controlled-release dosage forms in a therapeutically responsive dose over an extended period of time. Another embodiment of the invention pertains to a method for delivering a drug of the formula disclosed in this invention, to the gastrointestinal tract of a human in need of this therapy, wherein the method comprises the steps of: (A) admitting orally into the gastrointestinal tract of the human a dosage form comprising: (1) a non-toxic wall composition comprising means for imbibing an external aqueous fluid through the wall into the dosage form, which wall surrounds and defines; (2) an internal compartment; (3) a drug composition comprising a drug of the formula in the compartment comprising a dosage unit amount of said drug; (4) a push composition in the compartment for pushing the drug composition from the compartment; (5) at least one exit means in the wall for delivering the drug from the dosage form; (B) imbibing fluid through the wall into the compartment thereby causing the composition to form a deliverable dosage form and concomitantly causing the push composition to expand and push the drug composition through the exit means from the dosage form; and (C) deliver the therapeutic drug in a therapeutically effective amount at a controlled rate over an extended period of time to the patient in need of said therapy. The method also comprising dispensing a dose amount of said drug from an instant release exterior dosage amount of drug to the patient for providing instant anti-depressant therapy.

Inasmuch as the foregoing specification comprises preferred embodiments of the invention, it is understood that variations and modifications may be made herein, in accordance with the inventive principles disclosed, without departing from the scope of the invention.

We claim:

1. A method for administering a drug to the gastrointestinal tract of a human, wherein the method comprises:

(a) admitting orally into the human a dosage form comprising a drug of the formula:



which drug possess antidepressant therapy and the dosage form comprises a member selected from the group consisting of a sustained-release dosage form and a controlled-release dosage form; and,

(b) administering the drug from the dosage form over an extended period of time in a therapeutically responsive dose to produce the antidepressant therapy.

* * * * *

Exhibit 26

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re *Ex Parte* Reexamination of:	
United States Patent No. 6,440,457	Control No.: To Be Assigned
Inventors: David E. EDGREN *et al.*	Group Art Unit: To Be Assigned
Issue Date: August 27, 2002	
Application No. 08/068,480	Examiner: To Be Assigned
Filing Date: May 27, 1993	
For: METHOD OF ADMINISTERING ANTIDEPRESSANT DOSAGE FORM	

Mail Stop *Ex Parte* Reexam
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

REQUEST FOR *EX PARTE* REEXAMINATION

The undersigned respectfully requests an *ex parte* reexamination of United States Patent No. 6,440,457 ("the '457 patent"), which issued on August 27, 2002, to David E. Edgren *et al.* and lists Alza Corporation ("Alza") as the assignee. The '457 patent is a subject of the case *Alza Corp. v. Wyeth et al.*, Civil Action No. 9:06-cv-00156-RHC (E.D. Tex.). Pursuant to M.P.E.P. § 2219, a copy of the complaint in this pending action is attached as Exhibit B. There has not yet been a trial in the case.

This Request is accompanied by the following:

(1) The required fee of $2,520.00 under 37 C.F.R. § 1.20(c)(1);

(2) A statement pointing out each substantial new question of patentability based on the prior art;

(3) An identification of every claim for which reexamination is requested, and a detailed explanation of the pertinency and manner of applying the cited prior art to every claim for which reexamination is requested;

(4) A copy of each of the prior art references discussed in this Request and a listing thereof on Form PTO SB/08;

(5) A copy of the entire '457 patent (attached as Exhibit A) including the front face, drawings, and specification/claims, in double column format; and

(6) A certification that a copy of this Request for *Ex Parte* Reexamination in its entirety has been served on counsel of record, David J. Abraham, ALZA Corporation, 1900 Charleston Road, Mountain View, CA 94039, on July 28, 2006, via first class mail:

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TABLE OF EXHIBITS

Exhibit A	United States Patent No. 6,440,457, issued August 27, 2002.
Exhibit B	Complaint filed in *Alza Corp. v. Wyeth et al.*, Civil Action No. 9:06-cv-00156-RHC (E.D. Tex.).
Exhibit C	Board of Patent Appeals and Interferences Decision in Appeal No. 2005-1829 dated October 26, 2005.
Exhibit D	United States Patent No. 4,761,501, issued August 2, 1988 (*Husbands '501*).
Exhibit E	United States Patent No. 4,111,201, issued September 5, 1978 (*Theeuwes '201*).
Exhibit F	United States Patent No. 3,916,899, issued November 4, 1975 (*Theeuwes '899*).

I. Introduction

A. Identification of the Claim for Which Reexamination is Requested

Reexamination is requested for claim 1, the only claim of the '457 patent. A copy of the entire '457 patent is attached hereto as Exhibit A. This reexamination request requires consideration of the '457 patent and two of its child applications. Claim 1 of the '457 patent is directed to a method for administering venlafaxine to a human using sustained-release or controlled-release dosage forms to produce antidepressant therapy. United States Patent Application No. 08/442,292 ("the '292 application"), a divisional of the '457 patent, recites patentably indistinguishable composition claims directed to dosage forms for the delivery of venlafaxine. United States Patent Application No. 10/696,370 ("the '370 application"), a continuation of the '292 divisional application, also recites comparable claims directed to controlled-release and sustained-release dosage forms for venlafaxine delivery. The United States Patent and Trademark Office's ("PTO") rejection of these similar, patentably indistinguishable claims in the two child applications over prior art not considered during the examination of the '457 patent raises a substantial new question of patentability for claim 1 of the '457 patent.

B. Statement Pointing Out Substantial New Question of Patentability

In an October 26, 2005 decision (Exhibit C), the Board of Patent Appeals and Interferences ("Board") affirmed an obviousness rejection of claims that are indistinguishable for purposes of patentability from claim 1 of the '457 patent. The rejection at issue was based on two prior art patents, United States Patent No. 4,761,501 ("*Husbands '501*") (Exhibit D) and United States Patent No. 4,111,201 ("*Theeuwes '201*") (Exhibit E), the second of which the PTO did not consider during prosecution of the '457 patent. According to the Board, it would have been obvious to an ordinarily skilled artisan to formulate the antidepressants of *Husbands '501* in

the manner described in *Theeuwes '201* to arrive at a controlled-release formulation. The Board's rejection of these claims based upon a combination of references that was not considered during the examination resulting in the '457 patent raises a substantial new question of patentability with respect to the issued claim in that patent.

II. Background

This request for reexamination requires consideration of the '457 patent and the prosecution of two of its child applications claiming the benefit of the filing date of the application from which the '457 patent issued. As explained more fully below, in those child applications, the PTO has rejected claims that are similar to and indistinguishable for patentability purposes from claim 1 of the '457 patent over prior art not considered during the prosecution leading to the '457 patent. In fact, in one of these child applications, the Board affirmed the rejection and Alza did not appeal that decision to the Federal Circuit.

A. The '457 Patent

The '457 patent, entitled "Method of Administering Antidepressant Dosage Form," contains one claim directed to administering the antidepressant venlafaxine to a human. The '457 patent issued on August 27, 2002 from United States Patent Application No. 08/068,480 ("the '480 application"), which was filed on May 27, 1993. The '457 patent is assigned on its face to Alza Corporation.

1. The Specification of the '457 Patent

The '457 patent acknowledges that venlafaxine and its utility as an antidepressant were known before the May 27, 1993 filing date of the '457 patent.[1] The '457 patent disclosure provides that venlafaxine had a half-life of three to five hours and, therefore, had to be

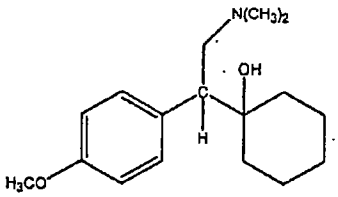
[1] '457 patent at column 6, lines 17-19 ("The compounds are known in U.S. Pat. Nos. 4,535,186; 4,611,078; 4,761,501; and 5,190,765"); column 6, lines 32-33 ("The drug embraced by the formula possesses antidepressant properties").

administered two to three times per day.[2] This dosing regimen caused undesirable peaks and valleys in the blood levels of venlafaxine.[3] According to the '457 patent, "[t]his pattern of dosing indicates the need for a controlled-release dosage form that can administer the drug at a controlled rate over an extended time to provide constant therapy and thereby eliminate the need for multiple dosing."[4] The '457 patent then identifies four Alza patents that describe dosage forms that provide "a controlled dose in a therapeutic range."[5] These dosage forms are, according to the '457 patent, not suitable for venlafaxine because its high solubility can result in its premature release.[6] The '457 patent purports to solve these problems by providing a formulation for "delivering the drug in a controlled-release rate from the dosage form."[7]

2. The Claim of the '457 Patent

Claim 1, the only claim of the '457 patent, recites:

> 1. A method for administering a drug to the gastrointestinal tract of a human, wherein the method comprises:
>
> (a) admitting orally into the human a dosage form comprising a drug of the formula:



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2 *Id.* at column 2, lines 19-20.

3 *Id.* at lines 16-18.

4 *Id.* at lines 21-24.

5 *Id.* at lines 28-41.

6 *Id.* at lines 44-52.

7 *Id.* at column 3, lines 28-30.

> which drug possess [sic] antidepressant therapy and the dosage form comprises a member selected from the group consisting of a sustained-release dosage form and a controlled-release dosage form; and,
>
> (b) administering the drug from the dosage form over an extended period of time in a therapeutically responsive dose to produce the antidepressant therapy.

3. The Prosecution History of the '457 Patent

The '480 application as originally filed contained seven claims, but, in response to a Restriction Requirement, Alza elected claim 4 (which ultimately issued as claim 1 in the '457 patent) for examination.[8] The Examiner rejected the elected claim as anticipated under 35 U.S.C. § 102(b) by United States Patent No. 3,916,899 ("*Theeuwes '899*") (Exhibit F),[9] stating that *Theeuwes '899* taught "oral administration" of "a control release device" and that "[d]rugs without limitation are disclosed."[10]

Alza responded to the rejection on February 7, 1995, arguing that "venlafaxine is not disclosed and it is not anticipated by Theeuwes '899."[11] Further, Alza contended that "[t]he Theeuwes '899 reference does not anticipate venlafaxine because its chemistry and physical properties are so unlike those drugs cited by Theeuwes '899."[12] One property cited by Alza was the "very high solubility" of venlafaxine.[13]

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8 Response to Restriction Requirement, paper #4, May 9, 1994, at 1.

9 Office Action, paper #5, August 26, 1994. The Examiner also rejected this claim under 35 U.S.C. § 112, second paragraph, as being indefinite. This rejection is not relevant here.

10 *Id.* at 2.

11 Amendment A, paper #7, February 7, 1995, at 3.

12 *Id.*

13 *Id.*

The Examiner disagreed. In a June 12, 1995, Final Office Action, he maintained the anticipation rejection of claim 4.[14] The Examiner noted that *Theeuwes '899* "successfully delivers sodium nitrate," a drug with "high solubility."[15] Accordingly, the Examiner reasoned, "it will deliver venlafaxine."[16]

On September 5, 1995, Alza submitted a Response, which, among other things, reiterated the arguments concerning the high solubility of venlafaxine.[17] Again, the Examiner disagreed with Alza's arguments,[18] and Alza appealed the final rejection of claim 4.[19]

The Board reversed, holding that "the examiner has not established that Theeuwes ['899] mentions venlafaxine by name," a disclosure needed to support an anticipation rejection.[20]

Just short of two years after the Board decision, the Examiner allowed claim 4 without a further rejection.[21] On August 27, 2002, the '457 patent issued, with claim 4 of the '480 application renumbered as patent claim 1.

B. United States Patent Application No. 08/442,292

On May 16, 1995, while the application for the '457 patent was pending, Alza filed a divisional application, United States Patent Application No. 08/442,292 ("the '292 application"). As explained below, the claims presented in the '292 application defined dosage forms

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14 Office Action, paper #8, June 12, 1995.

15 *Id.* at 3.

16 *Id.*

17 Amendment B, paper #9, September 5, 1995.

18 Advisory Action, paper #10, September 28, 1995.

19 Notice of Appeal from the Primary Examiner to the Board of Appeals, paper #12, December 11, 1995.

20 Decision of the Board of Patent Appeals and Interferences, Appeal No. 1996-3159, paper #17, April 20, 2000, at 3-4.

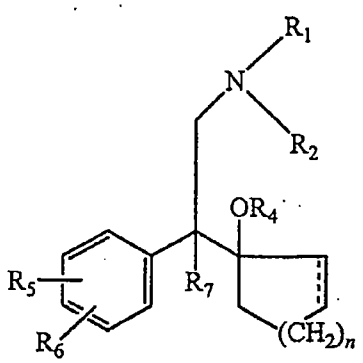
21 Notice of Allowability, paper #18, April 2, 2002.

purportedly useful in the method defined by claim 1 of the '457 patent and presented no meaningful distinction in terms of patentability from that claim. Critical to this Request for Reexamination, *the Board affirmed* an obviousness rejection of these claims based, in part, on prior art *not considered* during prosecution of the '457 patent.

1. The Prosecution History of Claims 6 and 7 of the '292 Application Before the Examiner

In Response to a Restriction Requirement, Alza elected claims 6 and 7 for examination in the '292 application. These claims both defined dosage forms for the oral delivery of a drug. Claim 6 defined the drug by a generic structural formula, which included venlafaxine. Claim 7 limited the drug to venlafaxine. Claims 6 and 7 recite:

> 6. A dosage form for the oral delivery of a drug to an environment of use, wherein the dosage form comprises:
>
> (a) a wall comprising at least in part a composition permeable to the passage of fluid, which wall surrounds:
>
> (b) a compartment;
>
> (c) a drug composition in the compartment comprising a drug of the formula:



> wherein the dotted line represents a member selected from the group consisting of an unsaturation and cycloalkenyl group; R_1 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbon atoms; R_2 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbon atoms; R_4 is a member selected from the group consisting of hydrogen,

> alkyl of 1 to 6 carbon atoms, formyl, and alkanoyl of 2 to 7 carbon atoms; R_5 and R_6 are independently a member selected from the group consisting of hydrogen, hydroxyl and alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, alknaoyloxy of 2 to 7 carbon atoms, nitro, alkylmercapto of 1 to 6 carbon atoms, amino, alkylamino of 1 to 6 carbon atoms, alkanamido of 2 to 7 carbon atoms, halo and trifluoroethyl; R_7 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbons; an [sic] n is 0 to 4; and
>
> (d) a displacement in the compartment comprising a composition comprising an osmotically active compound; and,
>
> (e) an exit passageway in the dosage form for delivering the drug composition from the dosage form.
>
> 7. A dosage form for the oral delivery of the drug to an environment of use according to claim 6, wherein the drug is 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]-cyclohexanol.[22]

In a January 25, 1996 Office Action, the Examiner rejected claims 6 and 7 under 35 U.S.C. § 102(b) as anticipated by *Theeuwes '899*, the same rejection made in the pending application for the '457 patent. The Examiner noted that *Theeuwes '899* "teaches an osmotic device comprising a compartment and a semipermeable wall" for the delivery of drugs, including "psychic energizers."[23] The Examiner also stated that venlafaxine "is well-known in the pharmaceutical art as an anti-depressant."[24]

Alza responded on May 29, 1996, arguing, among other things, that "venlafaxine is structurally and chemically unrelated to ... psychic energizers of the prior art."[25] In a September 4, 1996, Office Action, the Examiner withdrew the anticipation rejection, but rejected claims 6

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22 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]-cyclohexanol is the chemical name for venlafaxine.

23 Office Action, paper #4, January 25, 1996, at 4.

24 *Id.*

25 Amendment A, paper #6, May 29, 1996, at 4.

and 7 under 35 U.S.C. § 103(a) as obvious over *Husbands '501* in view of *Theeuwes '899*.[26] He made this rejection after the completion of briefing on the appeal of the '480 application.

In a March 4, 1997 Response, Alza argued that claims 6 and 7 were not obvious over the cited references because, *inter alia*, the "very high solubility" of venlafaxine teaches away from its use in the dosage form of *Theeuwes '899*.[27]

In a June 11, 1997 Office Action, the Examiner finally rejected claims 6 and 7 under 35 U.S.C. § 103(a) as obvious over *Husbands '501* in view of *Theeuwes '899*.[28] The Examiner stated that *Husbands '501* taught "substituted phenylacetamides such as venlafaxine as antidepressants" while *Theeuwes '899* taught an osmotic dosage form and "rate control" and that "[d]rugs without limitation are disclosed."[29] The Examiner also found that motivation to combine the references existed, but set forth no basis for this conclusion.[30]

Alza eventually appealed this rejection. On February 21, 2001, the Board, however, concluded that the case was "not in condition for a decision on appeal" because the Board could not determine the Examiner's position.[31] Consequently, it remanded the case to, among other things, clarify "the Examiner's reasons in support of unpatentability."[32] Significantly, the Board noted (1) the prior appeal in the '480 application, (2) its reversal of the anticipation rejection, and

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26 Office Action, paper #7, September 4, 1996.

27 Amendment B, paper #9, March 4, 1997, at 4.

28 Office Action, paper #10, June 11, 1997.

29 *Id.* at 2-3.

30 *Id.* at 3.

31 Decision of the Board of Patent Appeals and Interferences, Appeal No. 2000-1138, paper #25, February 21, 2001, at 1.

32 *Id.* at 3.

(3) the current pendency of that earlier application.[33] The Board then instructed the Examiner to "take an opportunity to review the merits of the two related cases and ***ensure that consistent action is taken in each.***"[34] Subsequent events demonstrate that the Examiner did not heed the Board's express instructions.

On remand, in an August 9, 2002 Office Action, the Examiner, citing new prior art and reopening prosecution, rejected claims 6 and 7 of the '292 application as obvious over *Husbands '501* in view of *Theeuwes '201*.[35] The Examiner stated, "[i]t would have been obvious to one of ordinary skill to deliver the antidepressant of [*Husbands '501*] in the vehicle of Theeuwes '201 to achieve the beneficial effect of delivery at a controlled rate."[36] In response to Applicants' assertions concerning the solubility of venlafaxine, the Examiner further stated that *Theeuwes '201* "teaches delivery of such highly soluble agents."[37] Significantly, despite the Board's instruction to "ensure that consistent action" be taken between the co-pending '480 and '292 applications, approximately four months before issuing this Office Action, the Examiner allowed the '480 application without considering the *Theeuwes '201* patent or rejecting the claims as obvious.

Alza responded to the rejection in the '292 application by arguing that "[w]hile [*Husbands '501*] may disclose venlafaxine and *Theeuwes* '201 a controlled release osmotic dosage form, there is no motivation in these cited references to combine these teachings."[38] Alza

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33 *Id.*

34 *Id.* at 3-4 (emphasis added).

35 Office Action, paper #26, August 9, 2002.

36 *Id.* at 2-3.

37 *Id.* at 3.

38 Response to Office Action, paper #27, December 19, 2002, at 5.

did not dispute that *Theeuwes '201* discloses a dosage form useful with highly soluble drugs. Instead, Alza again argued that the specific properties of venlafaxine, notably its "very high solubility," taught away from combining the references.[39]

The Examiner maintained the obviousness rejection in an April 28, 2003, Final Office Action Rejection. In response to Alza's solubility argument, the Examiner noted that *Theeuwes '201* "teaches delivery of highly soluble actives, a key teaching missing from the previously cited Theeuwes '899."[40] Alza appealed the final rejection.

2. The Board Decision Affirming the Examiner's Rejection of Claims 6 and 7 of the '292 Application on Obviousness Grounds

In an October 26, 2005 ruling, the Board affirmed the final rejection.[41] The Board found that *Husbands '501* and *Theeuwes '201* "teach each of the elements required by claim 6 on appeal," a finding that Alza did not dispute in its appeal brief.[42] Instead, Alza had argued no motivation to combine the teachings of the two references existed.[43]

The Board disagreed. In the Board's view, at least two teachings of *Theeuwes '201* provided the required motivation. The first stated "that the described dosage form provides for 'the controlled and continuous delivery of an active agent over a prolonged period of time which system overcomes the problems known to the prior art.'"[44] The second stated:

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39 *Id.*

40 Office Action, paper #28, April 28, 2003, at 3.

41 Decision of the Board of Patent Appeals and Interferences, Appeal No. 2005-1829, October 26, 2005.

42 *Id.* at 4.

43 Appellants' Brief, December 18, 2003, at 13.

44 Board Decision, Appeal No. 2005-1829, at 4.

> Yet [still] a further object of the invention is to provide an osmotic therapeutic system that can administer a complete pharmaceutical regimen comprising soluble to very soluble or limited soluble to practically insoluble agents at a constant rate to animals including warm blooded animals and humans for a particular time period, the use of which requires intervention only for initiation and possibly termination of the regimen.[45]

The Board also noted that *Theeuwes '201* "describes antidepressants as one of the active agents useful in the dosage form of the invention."[46] In light of these teachings, the Board held that "it would have been prima facie obvious to a person of ordinary skill in the art to formulate the antidepressants described in [*Husbands '501*] in the manner described in [*Theeuwes '201*] in order to arrive at an extended/controlled release formulation of that active agent."[47] Accordingly, it affirmed the rejection.

Because Alza grouped claims 6 and 7 together for purposes of the appeal, the Board did not address Alza's arguments concerning the properties of venlafaxine.

Alza abandoned the '292 application following the Board decision.

C. United States Patent Application No. 10/696,370

By the time of the Board decision dated October 26, 2005, Alza had already filed a continuation of the '292 application, United States Patent Application No. 10/696,370 ("the '370 application"). The '370 application now includes independent claims 9 and 15, each of which defines a venlafaxine-containing dosage form. Claim 9 recites:

> 9. A controlled-release dosage form for the oral delivery of 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]-cyclohexanol or its pharmaceutically acceptable salts to a patient, wherein the dosage form comprises:

---

45 *Id.*

46 *Id.*

47 *Id.* at 4-5.

> (a) a wall comprising a semipermeable composition permeable to the passage of fluid, but not to 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]-cyclohexanol or its pharmaceutically acceptable salts, which wall surrounds;
>
> (b) a compartment;
>
> (c) a therapeutic composition in the compartment comprising 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]-cyclohexanol or its pharmaceutically acceptable salts;
>
> (d) a displacement composition in the compartment comprising an osmotically effective compound; and,
>
> (e) an exit passageway in the dosage form for delivering the 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]-cyclohexanol from the dosage form in a controlled-release manner.

Claim 15 recites the same language as claim 9 except that it is directed to a "sustained-release dosage form." Although the claims in the '370 application limit the dosage form to one containing venlafaxine, the Examiner rejected these claims on the same basis and with the same art as the rejections affirmed by the Board in the '292 application. The claims presently stand finally rejected under 35 U.S.C. § 103(a) as obvious over *Husbands '501* in view of *Theeuwes '201*.[48]

Alza responded to the final Office Action on May 16, 2006, by setting forth five additional arguments for the patentability of claims 9 and 15.[49] The thrust of Alza's arguments was that *Theeuwes '201* does not teach a dosage form suitable to deliver a highly soluble drug such as venlafaxine within a therapeutic range over an extended period of time. Accordingly, Alza argued that *Theeuwes '201* "only teaches increasing the amount of drug delivered whereas

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[48] Office Action, March 16, 2006.

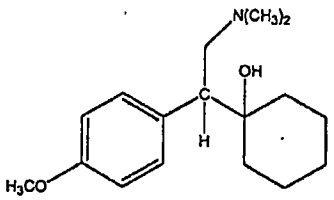
[49] Amendment/Response to Final Office Action, May 16, 2006. In the response, Alza also added claims 16-18 and 19-21, directed to three particular dosage ranges for the dosage forms recited in claims 9 and 15, respectively. In a June 7, 2006, Advisory Action, the Examiner indicated that the dosage range limitations did not place the application in condition for allowance because *Husbands* '501 and *Theeuwes* '201 "[b]oth encompass the now claimed amounts."

venlafaxine would require decreasing drug delivery."[50] Alza also argued that using venlafaxine in the dosage form of *Theeuwes '201* would result in premature drug release rather than release at a "controlled, zero-order rate."[51]

The Examiner rejected Alza's arguments.[52] In a June 7, 2006 Advisory Action, the Examiner noted that Alza's argument regarding *Theeuwes '201* teaching increased drug delivery "refers to the latter practically insoluble agents rather than the former very soluble agents."[53] The Examiner also rejected Alza's assertion that *Theeuwes '201* does not teach zero order release, stating that "Theeuwes '201 teaches such (column 5, line 59)."[54]

III. DETAILED EXPLANATION OF THE PERTINENCY AND APPLICATION OF THE PRIOR ART TO CLAIM 1

Claim 1 of the '457 patent defines a method for administering drug to the gastrointestinal tract of a human. It reads:

> 1. A method for administering a drug to the gastrointestinal tract of a human, wherein the method comprises:
>
> (a) admitting orally into the human a dosage form comprising a drug of the formula:
>
> 
>
>
> which drug possess [sic] antidepressant therapy and the dosage form comprises a member from the group consisting of a

50 Amendment/Response to Final Office Action, May 16, 2006, at 4.

51 *Id.* at 6-7.

52 Advisory Action, June 7, 2006.

53 *Id.* at 2.

54 *Id.*

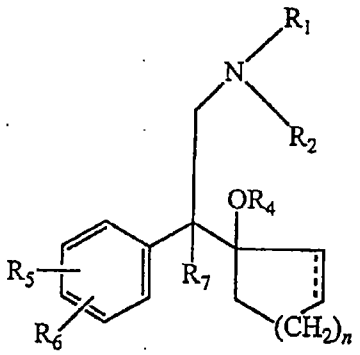
> sustained-release dosage form and a controlled-release dosage form; and,
>
> (b) administering the drug from the dosage form over an extended period of time in a therapeutically responsive dose to produce the antidepressant therapy.

As explained above, the Examiner had rejected this claim as anticipated by *Theeuwes '899*, and the Board reversed. Although the Board subsequently instructed the Examiner to take "consistent action" in examining the claim that ultimately issued as claim 1 of the '457 patent and the claims in the '292 application,[55] the Examiner allowed the '480 application to issue without further rejection. In contrast, the same Examiner rejected patentably indistinguishable claims 6 and 7 of the '292 application, which defined a dosage form for the oral delivery of a drug to an environment of use, as obvious over *Husbands '501* and *Theeuwes '201*. The Board affirmed that rejection. Claims 6 and 7 of the '292 application read as follows:

> 6. A dosage form for the oral delivery of a drug to an environment of use, wherein the dosage form comprises:
>
> (a) a wall comprising at least in part a composition permeable to the passage of fluid, which wall surrounds;
>
> (b) a compartment;
>
> (c) a drug composition in the compartment comprising a drug of the formula:

---

[55] See *page 13, supra.*



wherein the dotted line represents a member selected from the group consisting of an unsaturation and cycloalkenyl group; R_1 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbon atoms; R_2 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbon atoms; R_4 is a member selected from the group consisting of hydrogen, alkyl of 1 to 6 carbon atoms, formyl, and alkanoyl of 2 to 7 carbon atoms; R_5 and R_6 are independently a member selected from the group consisting of hydrogen, hydroxyl and alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, alknaoyloxy of 2 to 7 carbon atoms, nitro, alkylmercapto of 1 to 6 carbon atoms, amino, alkylamino of 1 to 6 carbon atoms, alkanamido of 2 to 7 carbon atoms, halo and trifluoroethyl; R_7 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbons; an n is 0 to 4; and

(d) a displacement in the compartment comprising a composition comprising an osmotically active compound; and,

(e) an exit passageway in the dosage form for delivering the drug composition from the dosage form.

7. A dosage form for the oral delivery of the drug to an environment of use according to claim 6, wherein the drug is 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]-cyclohexanol.[56]

Because of the relationship between claims 6 and 7 of the '292 application and claim 1 of the '457 patent, fundamental patent law dictates that a rejection applicable to claims 6 and 7

[56] 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]-cyclohexanol is the chemical name for venlafaxine.

should also apply to claim 1 of the '457 patent. Claim 1 of the '457 patent simply cannot be patentable if claims 6 and 7 are not. Since the Examiner did not consider *Theeuwes '201* during prosecution of the '457 patent and did not reject claim 1 of the '457 patent as obvious over a combination of *Husbands '501* and *Theeuwes '201*, there can be no dispute that the combined teachings of *Husbands '501* and *Theeuwes '201* raise a substantial new question of patentability as to claim 1 of the '457 patent.

This fact is buttressed by the Examiner's obviousness rejection of claims 9 and 15 in the '370 application over a combination of *Husbands '501* and *Theeuwes '201*. Claim 9 defines a controlled-release dosage form for the oral delivery of venlafaxine. It reads:

> A controlled-release dosage form for the oral delivery of 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]-cyclohexanol or its pharmaceutically acceptable salts to a patient, wherein the dosage form comprises:
>
> (a) a wall comprising a semipermeable composition permeable to the passage of fluid, but not to 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]-cyclohexanol or its pharmaceutically acceptable salts, which wall surrounds;
>
> (b) a compartment;
>
> (c) a therapeutic composition in the compartment comprising 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]-cyclohexanol or its pharmaceutically acceptable salts;
>
> (d) a displacement composition in the compartment comprising an osmotically effective compound; and,
>
> (e) an exit passageway in the dosage form for delivering the 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]-cyclohexanol from the dosage form in a controlled-release manner.

Claim 15 recites the same language as claim 9 except that it is directed to a "sustained-release dosage form." As in the case of the '292 application, a rejection of claims 9 and 15 should also apply to claim 1 of the '457 patent. The Examiner has rejected claims 9 and 15 of

the '370 application, which are limited to particular dosage forms for venlafaxine, as obvious over *Husbands '501* and *Theeuwes '201*, the same rejection he made for Claims 6 and 7 of the '292 application. Moreover, the Examiner has also rejected dependent claims in the '370 application that are further limited to specific dosage ranges of venlafaxine on the same grounds. While Alza purported to raise additional technical arguments suggesting that its *Theeuwes '201* patent was not enabled for highly soluble agents such as venlafaxine, the Examiner held those arguments to be unpersuasive in view of the explicit teaching of the '201 patent specification.[57] This additional rejection further demonstrates that the combination of *Husbands '501* and *Theeuwes '201* presents a substantial new question of patentability for claim 1 of the '457 patent.

IV. Conclusion

In view of the foregoing, Requester submits that the Examiner and the Board's analysis of prior art references not considered during the examination of the '457 patent, as well as the rejection of patentably indistinguishable claims in two child applications over these prior art references, raise substantial new questions of patentability for claim 1. It is therefore respectfully requested that this Request for *Ex Parte* Reexamination be granted at the PTO's earliest convenience and that a Reexamination Certificate be issued canceling claim 1 of the '457 patent.

[57] Advisory Action, June 7, 2006.

If there are any additional fees due in connection with the filing of this paper, please charge the required fees to our Deposit Account No. 08-0219.

Respectfully submitted,

WILMER CUTLER PICKERING
HALE AND DORR LLP

Dated: July 28, 2006

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Exhibit 27

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
90/008,142	09/06/2006	6440457	0002717-00264	6540

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EXAMINER	
Sharon L. Turner	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

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EX PARTE REEXAMINATION COMMUNICATION TRANSMITTAL FORM

REEXAMINATION CONTROL NO. 90/008142

PATENT NO. 6,440,457

ART UNI 3992

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above identified ex parte reexamination proceeding (37 CFR 1.550(f)).

Where this copy is supplied after the reply by requester, 37 CFR 1.535, or the time for filing a reply has passed, no submission on behalf of the ex parte reexamination requester will be acknowledged or considered (37 CFR 1.550(g)).

Office Action in Ex Parte Reexamination	Control No. 90/008,142	Patent Under Reexamination 6440457	
	Examiner Sharon L. Turner	Art Unit 3991	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

a☒ Responsive to the communication(s) filed on *01 December 2006* . b☐ This action is made FINAL.
c☐ A statement under 37 CFR 1.530 has not been received from the patent owner.

A shortened statutory period for response to this action is set to expire *1* month(s) from the mailing date of this letter. Failure to respond within the period for response will result in termination of the proceeding and issuance of an *ex parte* reexamination certificate in accordance with this action. 37 CFR 1.550(d). **EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.550(c).** If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☒ Information Disclosure Statement, PTO/SB/08.
3. ☐ Interview Summary, PTO-474.
4. ☐ _____.

Part II SUMMARY OF ACTION

1a. ☒ Claims *1* are subject to reexamination.
1b. ☐ Claims _____ are not subject to reexamination.
2. ☐ Claims _____ have been canceled in the present reexamination proceeding.
3. ☐ Claims _____ are patentable and/or confirmed.
4. ☒ Claims *1* are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ The drawings, filed on _____ are acceptable.
7. ☐ The proposed drawing correction, filed on _____ has been (7a)☐ approved (7b)☐ disapproved.
8. ☐ Acknowledgment is made of the priority claim under 35 U.S.C. § 119(a)-(d) or (f).
   a)☐ All b)☐ Some* c)☐ None of the certified copies have
   1☐ been received.
   2☐ not been received.
   3☐ been filed in Application No. _____ .
   4☐ been filed in reexamination Control No. _____.
   5☐ been received by the International Bureau in PCT application No. _____.
   * See the attached detailed Office action for a list of the certified copies not received.
9. ☐ Since the proceeding appears to be in condition for issuance of an *ex parte* reexamination certificate except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte* Quayle, 1935 C.D. 11, 453 O.G. 213.
10. ☐ Other: _____

cc: Requester (if third party requester)

Reexamination

Procedural History

1. A request for Reexamination was filed 7-28-06 by a third party requestor. A Notice of Failure to Comply with Ex Parte Reexamination Request Filing Requirements was mailed 8-23-06. A response to the Notice was filed 9-6-06 correcting the noted defects and thereby fulfilling all requirements. An order granting reexamination of claim 1 of the 6,440,457 ('457) patent was mailed 10-5-06. On 12-1-06 the following filings were received; an associate power of attorney, a request for change of correspondence address, a notice of concurrent litigation with attached court documents (which were not cited on a PTO-1449), an extensive PTO-1449 filed with references that were either newly cited references or references that were cited within the prosecution history of the '457 patent, and a notice of intent not to file Patent Owner's statement. This office action is the first office action on the merits in the reexamination of claim 1 of the '457 patent. It is noted that the record makes clear that the litigation pending in the United States District Court for the Eastern District of Texas captioned Alza Corp. v. Wyeth, et al., Civil Action No. 9:06-cv-00156-RHC ("the stayed litigation"), was **stayed** pending the outcome of this re-examination, see Order Granting Defendant's Motion to Stay, of the District Court on November 22, 2006.

Priority

2. US Patent 6,440,457 issued from US Application No. 08/068,480 filed 27 May 1993.

Background of the Prior Art

Gupta (Oral Controlled-Release Delivery)

Gupta reviews the general principles of oral controlled-release (CR) drug delivery sytsems and was published in 1992, prior to the '457 patents earliest priority date. The goal of oral CR products is to achieve better therapeutic success than with conventional dosage forms and this goal is realized by improving the pharmacokinetic profiles, patient convenience and compliance in therapy. Improved treatment is a major focus for diseases controlled by drugs that are used in chronic therapy regimes, such as with CNS agents. Gupta notes particular advantages of controlled-release formulations as delineated at pp. 256. Some of the advantages of oral CR dosage forms include; reduced dosing frequency, better patient convenience and compliance, reduced GI side effects and other toxic effects, less fluctuating plasma drug levels, more uniform drug effect, and lesser total dose. As in Gupta, the ideal system possesses all of these advantages. Gupta particularly notes continuous-release systems based on dissolution control, diffusion control, combined dissolution and diffusion control, ion-exchange resins, osmotically controlled devices, slow-dissolving salts or complexes, and pH-independence, see p. 284-299. Accordingly, Gupta is representative of the state of the art in formulating oral controlled-release systems and establishes the art-recognized advantages of formulating drug dosage forms for controlled-release delivery.

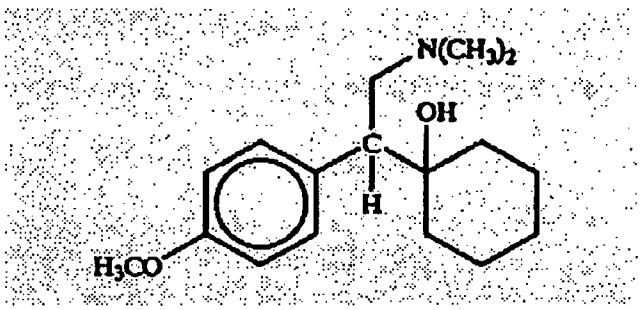
Longer (Sustained-Release Drug Delivery Systems)

Longer reviews the general principles of sustained-release drug delivery systems and was published in 1985. Longer notes the general goal of sustained-drug delivery systems including delivery of drug in a therapeutic amount to the proper site in the body, to timely achieve the required dose and then to maintain the proper concentration, see abstract. Longer further includes amongst sustained-release delivery systems both controlled release and prolonged release delivery, see p. 1645. Longer notes the particular advantages of sustained release delivery systems to include; avoid patient compliance problems, employ less total drug, minimize or eliminate local side effects, maintain or eliminate systemic side effects, obtain less potentiation or reduction in drug activity with chronic use, minimize drug accumulation with chronic dosing, improve efficiency in treatment, cure or control condition more promptly, improve control of condition, ie, reduce fluctuation in drug level, improve bioavailability of some drugs, make use of special effects, eg., sustained release aspirin for morning relief of arthritis by dosing before bedtime and economy. Longer also specifically notes regulation via dissolution control, diffusion control, ion-exchange resins, osmotically controlled devices, and pro-drug delivery devices for achieving sustained-drug delivery, see pp. 1650-1654. Accordingly, Longer is representative of the state of the art in formulating oral sustained-release systems and establishes the art-recognized advantages of formulating drug dosage forms for sustained-release delivery.

Scope of the 6,440,457 Patent Claim

3. Claim 1 is the only claim of the '457 patent and is under reexamination. Claim 1 is appended below.

1. A method for administering a drug to the gastrointestinal tract of a human, wherein the method comprises: (a) admitting orally into the human a dosage form comprising a drug of the formula:



which drug possess antidepressant therapy and the dosage form comprises a member selected from the group consisting of a sustained-release dosage form and a controlled-release dosage form; and, (b) administering the drug from the dosage form over an extended period of time in a therapeutically responsive dose to produce the antidepressant therapy.

The '457 patent distinguishes "sustained-release dosage form" and "controlled-release dosage form" within claim 1.

Looking to the '457 specification, "controlled-release forms" are described in the passages appended below.

Another object of the present invention is to provide a drug delivery **controlled-release** system that can deliver a drug for maintaining **constant drug levels** in the blood thereby functioning as a prolonged release system. (Column 3, lines 11-14)

The dosage form 10 of drawing FIG. 1 illustrates a **controlled-release** dosage form manufactured as an osmotic dosage form that delivers a drug by osmotic action over **an extended period of time**. The dosage form comprising controlled-release properties embraced by this invention are

successful at maintaining **substantially constant drug levels** in the blood or in a tissue. (Column 4, lines 21-27)

Further, the '457 specification describes "sustained-release dosage forms" as follows.

Another object of the present invention is to provide drug delivery sustained-release system that provides slow release of the drug over **an extended period of time optionally in a therapeutic range**. (Column 3, lines 15-18)

The dosage forms within the mode and manner of this invention comprises also sustained-release dosage forms. The sustained-release dosage forms releases the drug and provide drug levels in the blood or target tissue within **a therapeutic range over an extended period of time**. The invention embraces additionally pro-longed release dosage forms. The prolonged release dosage form denotes extended duration of drug delivery action over that achieved by conventional drug delivery. (Column 4, lines 27-36)

While these passages provide guidance to the use of the terms within the patent, the passages are descriptive, and are not defining or limiting. Accordingly both the terms appear to be consistent with the general status of the prior art with respect to formulating controlled-release and sustained-release formulations, see discussion above entitled Background of the Art. Accordingly, both terms may encompass the goal of achieving administration over an extended period of time. Further controlled release forms may achieve delivery within a constant level and sustained-release forms may provide delivery within a therapeutic range. It is further noted that the period of time which is interpreted as "extended" is not delineated by the specification or the claims of the '457 patent.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over **Husbands** (4,761,501) in view of **Montgomery** (J. Clin. Psych., 1993), **Gupta**, **Longer** and **Theeuwes** (4,111,201).

Husbands teaches substituted phenylacetamides such as venlafaxine (1-{-2-dimethyl-amino)-1-(4-methoxyphenyl)-ethyl]cyclohexanol) which are useful as CNS antidepressants, see in particular description, compound A and Examples 3 and 33. Husbands notes various methods of preparation as well as pharmaceutical compositions, see in particular columns 2-7, Examples and column 10, line 18-column 11, line 10. The effectiveness of the antidepressant activity is assessed as noted at column 8, lines 11-40 via administering the drug to a human subject. Kinetic dose-response relationships of the drug are noted at columns 8-10. Particularly, administration includes an oral dose to a human from about 2 to about 50 milligrams administered "as needed", see passage at column 10, lines 17-31. Further guidance to the oral formulation is taught for example in oral dosage form such as tablets, capsules

or liquid preparations, see column 10, lines 33-63. Unit dosage forms are further provided in the paragraph spanning columns 10-11.

Accordingly, the **Husbands** reference teaches administration of venflaxine to the gastrointestinal tract of the human, the drug possesses antidepressant therapy, the dosage form is any of the normal dosage forms as stipulated in **Husbands** and is administered as needed so as to eliminate depressive symptoms in the patient and to successfully produce antidepressant therapy. However, the guidance of **Husbands** does not ipsis verbis teach a "**sustained-release dosage form and a controlled-release dosage form**" as recited in element (a) nor does it specify that the administration is "**over an extended period of time**" as recited in element (b).

Montgomery is a review reference reporting a symposium on venflaxine treatment for depression held in Nice, France on June 28, 1992. The publication summarizes data from multiple laboratory and clinical trials and was published in the January 1993 issue of the Journal of Clinical Psychiatry with library receipt date of February 16, 1993. At pp. 121, column 3, the reference notes advantages of venlafaxine including having a rapid onset of action, more benign side-effects, a better cardiac conduction profile, and at least equivalent efficacy in treating depression in patients. **Montgomery** also notes a rapid-onset adrenergic subsensitivity in animals that occurs after a single administration. A summary of animal study data and a basis for the drug's activity in the treatment of depression is measured by various laboratory and neurobehavioral tests, see findings at p. 122. Human clinical trial data is summarized throughout pp. 122-124 including the disclosure of relevant dosage ranges

for either twice daily or thrice daily administration and at low or high dose treatment, generally ranging from 25-375 mg/day as specified in different regimes. These studies include treatment over an extended period of time including up to 96-weeks. At pp. 125-126. **Montgomery** further summarizes data relevant to long-term safety and tolerance and includes a review of studies with patients in treatment for up to one year. Montgomery concludes that there is evidence for an early onset of action and superior efficacy in controlled trials with venflaxine for the treatment of depression.

In summary, **Montgomery** teaches the skill of the artisan in determining administration of venflaxine "as needed". The dosage ranges and periods of time were disclosed and were known to the artisan prior to the '457 patent's earliest priority date. Montgomery acknowledges the art recognized successful treatment of depression in humans and evidences the prolonged maintenance of constant and therapeutic drug levels, effective to treat depression, and over extended periods of time including at rates from 25 to 375 mg/day and times for up to at least one year.

Accordingly, one of skill in the art would be motivated to provide treatment with venflaxine to depressed human patients at dosage rates and times consistent with the successful clinical trials disclosed in **Montgomery**, thereby arriving at treatment consistent with the claimed invention including administration that is "**over an extended period of time**," particularly including for at least one year. The Examiner would argue that this administration is also sufficient to meet the "**sustained-release dosage form and a controlled-release dosage form**" as the treatment notes administration of a constant amount of drug, for example at 75-375 mg/day t.i.d, which is maintained within

the therapeutic range and over an extended period of time to successfully treat depression.

While **Montgomery** supplements **Husbands** with respect to the clarification of what administration on an "as needed" basis specifically entails. One might still argue that the treatment with venflaxine consistent with the administration protocol of **Husbands** and **Montgomery** does not arrive at a "**sustained-release dosage form and a controlled-release dosage form**" as the references do not ipsis verbis recite such dosage forms as claimed.

Accordingly, the teachings of **Gupta** and **Longer** are noted as set forth above. The artisan is motivated to provide **sustained and controlled release dosage forms** for any of the art recognized advantages that these formulations provide. In particular, **Gupta** teaches the advantages of reduced dosing frequency, better patient convenience and compliance, reduced GI side effects and other toxic effects, less fluctuating plasma drug levels, more uniform drug effect, and lesser total dose. **Longer** further teaches the art recognized advantages of avoid patient compliance problems, employ less total drug, minimize or eliminate local side effects, maintain or eliminate systemic side effects, obtain less potentiation or reduction in drug activity with chronic use, minimize drug accumulation with chronic dosing, improve efficiency in treatment, cure or control condition more promptly, improve control of condltion, ie, reduce fluctuation in drug level, improve bioavailability of some drugs, make use of special effects, eg., sustained release aspirin for morning relief of arthritis by dosing before bedtime and economy. All of these advantages provide motivation for the artisan to combine the treatment of

Husbands and **Montgomery** in particularly formulated sustained-release and controlled-release dosage forms, specifically for the purpose of circumventing the noted rapid-onset adrenergic subsensitivity, to improve ease of compliance via reducing the need to dose twice or thrice daily, to reduce the occurrence of side-effects and to achieve maximal bioavailability without excess administration, thereby achieving maximal efficacy and economy.

Gupta and **Longer** teach preferred osmotic systems such as the **Theeuwes** device to achieve these sustained-release and controlled-release forms of drug admisitration.

In particular, **Theeuwes** teaches an osmotic delivery system for drug agents having **varying degrees of solubility** and specifically teaches that the system is useful for administration of **anti-depressants drugs to humans at a continuous and controlled rate**, see in particular columns 1-2, particularly column 2, lines 39-46, column 10, lines 9-29 and claim 16. The osmotic system is for **controlled and continuous delivery over** time to humans, see column 2, lines 39-46, column 3, lines 14-16 and claim 1. Example 5 also particularly notes the system manufactured as an **oral device** for delivery to the **gastrointestinal tract**. **Theeuwes** also particularly notes that the system is suitable for delivery of drug agents that are **very soluble** or practically insoluble as the venflaxine drug is noted to be, see columns 1-2, particularly column 2, lines 39-46. Accordingly, the Theeuwes device applies as a **sustained-release dosage form and a controlled-release dosage form** within the context of the

'457 patent claim, and the delivery is at **a continuous and controlled rate over a prolonged period of time.**

Thus, one of skill in the art would be motivated to provide treatment with venflaxine to depressed patients consistent with the dosage guidance provided in **Husbands** and **Montgomery**. The venflaxine treatment of depression is particularly noted to be one that extends over a long period of time, including constant level administration for at least a year and perhaps longer. An osmotic dosage delivery system as taught by **Theeuwes** is recognized as set forth above as suitable to achieve administration of antidepressant drugs to patients in a form that is consistent with a **sustained-release and controlled release dosage form.** Accordingly the artisan would be motivated to use the **Theeuwes** device to achieve **sustained-release and controlled release** delivery of drug to the depressed patient and provide the art recognized advantages of; reduced dosing frequency, better patient convenience and compliance, reduced GI side effects and other toxic effects, less fluctuating plasma drug levels, more uniform drug effect, and lesser total dose as suggested by **Gupta**, to avoid patient compliance problems, employ less total drug, minimize or eliminate local side effects, maintain or eliminate systemic side effects, obtain less potentiation or reduction in drug activity with chronic use, minimize drug accumulation with chronic dosing, improve efficiency in treatment, cure or control condition more promptly, improve control of condition, ie, reduce fluctuation in drug level, improve bioavailability of some drugs, make use of special effects, eg., sustained release aspirin for morning relief of arthritis by dosing before bedtime and increase economy as suggested by **Longer**, and to

achieve controlled and continuous rate delivery of highly soluble antidepressant drugs to human patients, over an extended period of time as required in the treatment of depression as suggested by **Theeuwes**. Accordingly, the cumulative reference teachings render the claimed invention obvious to the skilled artisan.

Conclusion

6. Claim 1 is rejected.

Patent Owner Amendment

7. Patent owner is notified that any proposed amendment to the specification and/or claims in this reexamination proceeding must comply with 37 CFR 1.530(d)-(j), must be formally presented pursuant to 37 CFR 1.52(a) and (b), and must contain any fees required by 37 CFR 1.20(c).

Duty to Disclose

8. The patent owner is reminded of the continuing responsibility under 37 CFR 1.565(a) to apprise the Office of any litigation activity, or other prior or concurrent proceeding, involving Patent No 6,440,457 throughout the course of this reexamination proceeding. The third party requester is also reminded of the ability to similarly appraise the Office of any such activity or proceeding throughout the course of this reexamination proceeding. See MPEP §§ 2207, 2282 and 2286.

Extension of Time

9. Extensions of time under 37 CFR 1.136(a) will not be permitted in these proceedings because the provisions of 37 CFR 1.136 apply only to "an applicant" and

not to parties in a reexamination proceeding. Additionally, 35 U.S.C. 305 requires that ex parte reexamination proceedings "will be conducted with special dispatch" (37 CFR 1.550(a)). Extensions of time in ex parte reexamination proceedings are provided for in 37 CFR 1.550(c).

Future Correspondence

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon Turner whose telephone number is 571-272-0894. The examiner can normally be reached on Monday through Thursday from 7:00 a.m. to 5:00 p.m. If the attempts to reach the examiner are unsuccessful, the examiner's supervisor, Deborah Jones can be reached by dialing 571-272-1535. The official fax number for the organization where this application is assigned is 571-273-9900.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

11. **All** correspondence relating to this *ex parte* reexamination proceeding should be directed as follows:

By **U.S. Postal Service Mail** to:

Mail Stop *Ex Parte* Reexam
ATTN: Central Reexamination Unit
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

By FAX to: (571) 273-9900
Central Reexamination Unit

By hand to: Customer Service Window
Randolph Building
401 Dulany St.
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Exhibit 28

90/008,142 METHOD OF ADMINISTERING ANTIDEPRESSANT DOSAGE FORM 11-30-2007::00:46:11

This application is officially maintained in electronic form. To View: Click the desired Document Description. To Download and Print: Check the desired document(s) and click Start Download.

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EXHIBIT 29 - 32
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Exhibit 33

US006403120B1

(12) **United States Patent**
Sherman et al.

(10) **Patent No.: US 6,403,120 B1**
(45) **Date of Patent: Jun. 11, 2002**

(54) **EXTENDED RELEASE FORMULATION OF VENLAFAXINE HYDROCHLORIDE**

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(63) Continuation of application No. 09/884,412, filed on Jun. 19, 2001, which is a division of application No. 09/488,629, filed on Jan. 20, 2000, now Pat. No. 6,274,171, which is a continuation-in-part of application No. 08/964,328, filed on Nov. 5, 1997, now abandoned, which is a continuation-in-part of application No. 08/821,137, filed on Mar. 20, 1997, now abandoned.

(60) Provisional application No. 60/014,006, filed on Mar. 25, 1996.

(51) **Int. Cl.**[7] **A61K 9/52**; A61K 9/54; A61K 9/62

(52) **U.S. Cl.** **424/461**; 424/457; 424/458; 424/459; 514/781; 514/962

(58) **Field of Search** 424/461, 458, 424/459, 457, 456, 462, 494, 495

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(57) **ABSTRACT**

This invention relates to a 24 hour extended release dosage formulation and unit dosage form thereof of venlafaxine hydrochloride, an antidepressant, which provides better control of blood plasma levels than conventional tablet formulations which must be administered two or more times a day and fiber provides a lower incidence of nausea and vomiting than the conventional tablets. More particularly, the invention comprises an extended release formulation of venlafaxine hydrochloride comprising a therapeutically effective amount of venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and, optionally, hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose.

14 Claims, No Drawings

EXTENDED RELEASE FORMULATION OF VENLAFAXINE HYDROCHLORIDE

This application is a continuation of Ser. No. 09/884,412, filed Jun. 19, 2001, which is a a divisional application of Ser. No. 09/488,629, filed Jan. 20, 2000, now U.S. Pat. No. 6,274,171, which is a continuation-in-part of Application Ser. No. 08/964,328, filed Nov. 5, 1997, now abandoned, which is a continuation-in part of Application No. 08/821, 137, filed Mar. 20, 1997, now abandoned, which claims priority from Provisional Application No. 60/014,006 filed Mar. 25, 1996.

BACKGROUND OF THE INVENTION

Extended release drug formulations are conventionally produced as compressed tablets by hydrogel tablet technology. To produce these sustained release tablet drug dosage forms, the active ingredient is conventionally compounded with cellulose ethers such as methyl cellulose, ethyl cellulose or hydroxypropylmethylcellulose with or without other excipients and the resulting mixture is pressed into tablets. When the tablets are orally administered, the cellulose ethers in the tablets swell upon hydration from moisture in the digestive system, thereby limiting exposure of the active ingredient to moisture. As the cellulose ethers are gradually leached away by moisture, water more deeply penetrates the gel matrix and the active ingredient slowly dissolves and diffuses through the gel, making it available for absorption by the body. An example of such a sustained release dosage form of the analgesic/anti-inflammatory drug etodolac (Lodin) appears in U.S. Pat. No. 4,966,768. U.S. Pat. No. 4,389,393 discloses sustained release therapeutic compressed solid unit dose forms of an active ingredient plus a carrier base comprised of a high molecular weight hydroxypropylmethylcellulose, methyl cellulose, sodium carboxymethylcellulose and or other cellulose ether.

Where the production of tablets is not feasible, it is conventional in the drug industry to prepare encapsulated drug formulations which provide extended or sustained release properties. In this situation, the extended release capsule dosage forms may be formulated by mixing the drug with one or more binding agents to form a uniform mixture which is then moistened with water or a solvent such as ethanol to form an extrudable plastic mass from which small diameter, typically 1 mm, cylinders of drug/matrix are extruded, broken into appropriate lengths and transformed into spheroids using standard spheronization equipment. The spheroids, after drying, may then be thin-coated to retard dissolution. The fin-coated spheroids may then be placed in pharmaceutically acceptable capsules, such as starch or gelatin capsules, in the quantity needed to obtain the desired therapeutic effect. Spheroids releasing the drug at different rates may be combined in a capsule to obtain desired release rates and blood levels. U.S. Pat. No. 4,138, 475 discloses a sustained release pharmaceutical composition consisting of a hard gelatin capsule filled with film-coated spheroids comprised of propanolol in admixture with microcrystalline cellulose wherein the film coating is composed of ethyl cellulose, optionally, with hydroxypropylmethylcellulose and/or a plasticizer.

Venlafaxine, 1-[2-(dimethylamino)-1-(4methoxyphenyl) ethyl]cyclohexanol, is an important drug in the neuropharmacological arsenal used for treatment of depression. Venlafaxine and the acid addition salts thereof are disclosed in U.S. Pat. No. 4,535,186. Venlafaxine hydrochloride is presently administered to adults in compressed tablet form in

doses ranging from 75 to 350 mg/day, in divided doses two or three times a day. In therapeutic dosing with venlafaxine hydrochloride tablets, rapid dissolution results in a rapid increase in blood plasma levels of the active compound shortly after administration followed by a decrease in blood plasma levels over several hours as the active compound is eliminated or metabolized, until sub-therapeutic plasma levels are approached after about twelve hours following administration, thus requiring additional dosing with the drug. With the plural daily dosing regimen the most common side effect is nausea, experienced by about forty five percent of patients under treatment with venlafaxine hydrochloride. Vomiting also occurs in about seventeen percent of the patients.

BRIEF DESCRIPTION OF THE INVENTION

In accordance with this invention, there is provided an extended release (ER), encapsulated formulation containing venlafaxine hydrochloride as the active drug component, which provides in a single dose, a therapeutic blood serum level over a twenty four hour period.

Through administration of the venlafaxine formulation of this invention, there is provided a method for obtaining a flattened drug plasma concentration to time profile, thereby affording a tighter plasma therapeutic range control than can be obtained with multiple daily dosing. In other words, this invention provides a method for eliminating the sharp peaks and troughs hills and valleys) in blood plasma drug levels induced by multiple daily dosing with conventional immediate release venlafaxine hydrochloride tablets. In essence, the plasma levels of venlafaxine hydrochloride rise, after administration of the extended release formulations of this invention, for between about five to about eight hours (optimally about six hours) and then begin to fall through a protracted, substantially linear decrease from the peak plasma level for the remainder of the twenty four hour period, maintaining at least a threshold therapeutic level of the drug during the entire twenty-four period. In contrast, the conventional immediate release venlafaxine hydrochloride tablets give peak blood plasma levels in 2 to 4 hours. Hence, in accordance with the use aspect of this invention, there is provided a method for moderating the -plural blood plasma peaks and valleys attending the pharmacokinetic utilization of multiple daily tablet dosing with venlafaxine hydrochloride which comprises administering to a patient in need of treatment with venlafaxine hydrochloride, a one-a-day, extended release formulation of venlafaxine hydrochloride.

The use of the one-a-day venlafaxine hydrochloride formulations of this invention reduces by adaptation, the level of nausea and incidence of emesis that attend the administration of multiple daily dosing. In clinical trials of venlafaxine hydrochloride ER, the probability of developing nausea in the course of the trials was greatly reduced after the first week. Venlafaxine ER showed a statistically significant improvement over conventional venlafaxine hydrochloride tablets in two eight-week and one 12 week clinical studies. Thus, in accordance with this use aspect of the invention there is provided a method for reducing the level of nausea and incidence of emesis attending the administration of venlafaxine hydrochloride which comprises dosing a patient in need of treatment with venlafaxine hydrochloride with an extended release formulation of venlafaxine hydrochloride once a day in a therapeutically effective amount.

The formulations of this invention comprise an extended release formulation of venlafaxine hydrochloride compris-

ing a therapeutically effective amount of venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and, optionally, hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose. Unless otherwise noted, the percentage compositions mentioned herein refer to percentages of the total weight of the final composition or formulation.

More particularly, the extended release formulations of this invention are those above wherein the spheroids are comprised of from about 6% to about 40% venlafaxine hydrochloride by weight, about 50% to about 95% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

A preferred embodiment of this invention are formulations wherein the spheroids are comprised of about 30% to about 40% venlafaxine hydrochloride by weight, about 50% to about 70% microcrystalline cellulose, NT, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

Another preferred lower dose formulation of this invention are those wherein the spheroids are comprised less than 30% venlafaxine hydrochloride. These formulations comprise spheroids of from about 6% to about 30% venlafaxine hydrochloride by weight, about 70% to about 94% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

Within this subgroup of lower dose formulations are formulations in which the spheroids are comprised of from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. Another preferred subgroup of spheroids in these formulations comprises from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. A ether preferred subgroup of spheroids in these formulations comprises from about 6% to about 20% venlafaxine hydrochloride and from about 94% to about 80% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. Within each of these subgroups is understood to be formulations in which the spheroids are comprised of venlafaxine HCT and microcrystalline cellulose in the amounts indicated, with no hydroxypropylmethylcellulose present. Each of these formulations is also preferably contained in a gelatin capsule, preferably a bard gelatin capsule.

DETAILED DESCRIPTION OF THE INVENTION

1-[2-(dimethylamino)-1-(4methoxyphenyl)ethyl] cyclohexanol hydrochloride is polymorphic. Of the forms isolated and characterized to date, Form I is considered to be the kinetic product of crystallization which can be converted to Form II upon heating in the crystallization solvent. Forms I and II cannot be distinguished by their melting points but do exhibit some differences in their infrared spectra and X-ray diffraction patterns. Any of the polymorphic forms such as Form I or Form II may be used in the formulations of the present invention.

The extended release formulations of this invention are comprised of 1-[2-(dimethylamino)-1-(4-methoxyphenyl) ethyl]cyclohexanol hydrochloride in admixture with microcrystalline cellulose and hydroxypropylmethylcellulose. Formed as beads or spheroids, the drug containing formulation is coated with a mixture of ethyl cellulose and hydroxypropylmethyl cellulose to provide, the desired level of coating, generally from about two to about twelve percent on a weight/weight basis of final product or more preferably from about five to about ten percent (w/w), with best results obtained at from about 6 to about 8 percent (w/w). More specifically, the extended release spheroid formulations of this invention comprise from about 30 to 40 percent venlafaxine hydrochloride, from about 50 to about 70 percent microcrystalline cellulose, NF, from about 0.25 to about 1 percent hydroxypropylmethylcellulose, USP, and from about 5 to about 10 percent film coating, all on a weight/weight basis. And preferably, the spheroid formulations contain about 35 percent venlafaxine hydrochloride, about 55 to 60 percent microcrystalline cellulose NF (Avicel® PH101), about one half percent hydroxypropylmethylcellulose 2208 USP (K3, Dow, which has a viscosity of 3 cps for 2% aqueous solutions, a methoxy content of 19–24% and a hydroxypropoxy content of 4–13%), and from about 6 to 8 percent film coating.

The film coating is comprised of 80 to 90 percent of ethyl cellulose, NF and 10 to 20 percent hydroxypropylmethylcellulose (2910), USP on a weight/weight basis. Preferably the ethyl cellulose has a ethoxy content of 44.0–51% and a viscosity of 50 cps for a 5% aqueous solution and the hydroxypropylmethylcellulose is USP 2910 having a viscosity of 6 cps at 2% aqueous solution with a methoxy content of 28–30% and a hydroxypropoxy content of 7–12%. The ethyl cellulose used herein is Aqualon HG 2834.

Other equivalents of the hydroxypropylmethylcelluloses 2208 and 2910 USP and ethyl cellulose, NF, having the same chemical and physical characteristics as the proprietary products named above may be substituted in the formulation without changing the inventive concept. Important characteristics of suitable hydroxypropylmethylcelluloses include a low viscosity, preferably less than 10 cps and more preferably 2–5 cps, and a gel temperature above that of the temperature of the extrudate during extrusion. As explained below, these and other characteristics which enable the extrudate to remain moist and soft (pliable) are preferred for the hydroxypropylmethylcellulose. In the examples below, the extrudate temperature was generally 50–55° C.

It was completely unexpected that an extended release formulation containing venlafaxine hydrochloride could be obtained because the hydrochloride of venlafaxine proved to be extremely water soluble. Numerous attempts to produce extended release tablets by hydrogel technology proved to be fruitless because the compressed tablets were either physically unstable (poor compressibility or capping problems) or dissolved too rapidly in dissolution studies. Typically, the tablets prepared as hydrogel sustained release formulations gave 40–50% dissolution at 2 hrs, 60–70% dissolution at 4 hrs and 85–100% dissolution at 8 hrs.

Numerous spheroid formulations were prepared using different grades of microcrystalline cellulose and hydroxypropylmethylcellulose, different ratios of venlafaxine hydrochloride and filler, different binders such as polyinylpyrrolidone, methylcellulose, water, and polyethylene glycol of different molecular weight ranges in order to find a formulation which would provide a suitable granulation mix which could be extruded properly. In the extrusion process, heat buildup occurred which dried out the extrudate so much that it was difficult to convert the extruded cylinders into spheroids. Addition of hydroxypropylmethylcellulose 2208 -to the venlafaxine hydrochloride-microcrystalline cellulose mix made production of spheroids practical.

The encapsulated formulations of this invention may be produced in a uniform dosage for a specified dissolution profile upon oral administration by techniques understood in the art. For instance, the spheroid components may be blended for uniformity with a desired concentration of active ingredient, then spheronized and dried. The resulting spheroids can then be sifted through a mesh of appropriate pore size to obtain a spheroid batch of uniform and prescribed size.

The resulting spheroids can be coated and resifted to remove any agglomerates produced in the coating steps. During the coating process samples of the coated spheroids may be tested for their distribution profile. If the dissolution occurs too rapidly, additional coating may be applied until the spheroids present a desired dissolution rate.

The following examples are presented to illustrate applicant's solution to the problem of preparation of the extended release drug containing formulations of this invention.

EXAMPLE NO. 1

Venlafaxine Hydrochloride Extended Release Capsules

A mixture of 44.8 parts (88.4% free base) of venlafaxine hydrochloride, 74.6 parts of the microcrystalline cellulose, NF, and 0.60 parts of hydroxypropylmethyl cellulose 2208, USP, are blended with the addition of 41.0 parts water. The plastic mass of material is extruded, spheronized and dried to provide uncoated drug containing spheroids.

Stir 38.25 parts of ethyl cellulose, NF, HG2834 and 6.75 parts of hydroxypropylmethylcellulose 2910, USP in a 1:1 v/v mixture of methylene chloride and anhydrous methanol until solution of the film coating material is complete.

To a fluidized bed of the uncoated spheroids is applied 0.667 parts of coating solution per part of uncoated spheroids to obtain extended release, film coated spheroids having a coating level of 3%.

The spheroids are sieved to retain the coated spheroids of a particle size between 0.85 mm to 1.76 mm diameter. These selected film coated spheroids are filled into pharmaceutically acceptable capsules conventionally, such as starch or gelatin capsules.

EXAMPLE NO. 2

Same as for Example 1 except that 1.11 parts of the film coating solution per part of uncoated spheroids is applied to obtain a coating level of 5%.

EXAMPLE NO. 3

Same as for Example 1 except that 1.33 parts of the film coating solution is applied to 1 part of uncoated spheroids to obtain a coating level of 6%.

EXAMPLE NO. 4

Same as for Example 1 except that 1.55 parts of the film coating solution is applied to 1 part of uncoated spheroids to obtain a coating level of 7%.

In the foregoing failed experiments and in Examples 1–4, the extrusion was carried out on an Alexanderwerk extruder. Subsequent experiments carried out on Hutt and Nica extruders surprisingly demonstrated that acceptable, and even improved, spheroids could be made without the use of an hydroxypropylmethylcellulose.

In such fierier experiments the applicability of the invention was extended to formulations wherein the weight percentage of venlafaxine hydrochloride is 6% to 40%, preferably 8% to 35%. Thus, the extended release spheroid formulations of this invention comprise from about 6 to about 40 percent venlafaxine hydrochloride, from about 50 to about 94 percent microcrystalline cellulose, NF, optionally, from about 0.25 to about 1 percent hydroxypropylmethylcellulose, and from about 2 to about 12 percent, preferably about 3 to 9 percent, film coating.

Spheroids of the invention were produced having 8.25% (w/w) venlafaxine hydrochloride and the remainder (91.75%, w/w) being microcrystalline cellulose, with a coating of from 3 to 5% (w/w), preferably 4%, of the total weight. The spheroids with 8.25% venlafaxine hydrochloride and 4% coating were filled into No. 2 white opaque shells with a target fill weight of 236 mg.

Further spheroids of the invention were produced having 16.5% (w/w) venlafaxine hydrochloride and the remainder (83.5%,w/w) being microcrystalline cellulose, with a coating of from 4 to 6% (w/w), preferably 5%, of the total weight. The spheroids 16.5% venlafaxine hydrochloride and 5% coating were filled into No. 2 white opaque shells with a target fill weight of 122 mg.

The test for acceptability of the coating level is determined by analysis of the dissolution rate of the finished coated spheroids prior the encapsulation. The dissolution procedure followed uses USP Apparatus 1 (basket) at 100 rpm in purified water at 37° C.

Conformance with the dissolution rate given in Table 1 provides the twenty-four hour therapeutic blood levels for the drug component of the extended release capsules of this invention in capsule form. Where a given batch of coated spheroids releases drug too slowly to comply with the desired dissolution rate study, a portion of uncoated spheroids or spheroids with a lower coating level may be added to the batch to provide, after thorough mixing, a loading dose for rapid increase of blood drug levels. A batch of coated spheroids that releases the drug too rapidly can receive additional film-coating to give the desired dissolution profile.

TABLE 1

Acceptable Coated Spheroid Dissolution Rates

Time (hours)	Average % Venlafaxine HCl released
2	<30
4	30–55
8	55–80
12	65–90
24	>30

Batches of the coated venlafaxine hydrochloride containing spheroids which have a dissolution rate corresponding to that of Table 1 are filled into pharmaceutically acceptable capsules in an amount needed to provide the unit dosage level desired. The standard unit dosage immediate release (IR) tablet used presently provides amounts of venlafaxine hydrochloride equivalent to 25 mg, 37.5 mg, 50 mg, 75 mg and 100 mg venlafaxine. The capsules of this invention are

filled to provide an amount of venlafaxine hydrochloride equivalent to that presently used in tablet form and also up to about 150 mg venlafaxine hydrochloride.

Dissolution of the venlafaxine hydrochloride ER capsules is determined as directed in the U.S. Pharmacopoeia (JSP) using apparatus 1 at 100 rpm on 0.9 L of water. A filtered sample of the dissolution medium is taken at the times specified. The absorbance of the clear solution is determined from 240 to 450 nanometers (nm) against the dissolution medium. A baseline is drawn from 450 am through 400 nm and extended to 240 nm. The absorbance at the wavelength of maximum absorbance (about 274 mm) is determined with respect to this baseline. Six hard gelatin capsules are filled with the theoretical amount of venlafaxine hydrochloride spheroids and measured for dissolution. Standard samples consist of venlafaxine hydrochloride standard solutions plus a gelatin capsule correction solution.

The percentage of venlafaxine released is determined from the equation

$$\%\ \text{Venlafaxine hydrochloride released} = \frac{(As)(Wr)(S)(Vl)(0.888)(100)}{(Ar)(V2)(C)}$$

where As is absorbance of sample preparation, Wr is weight of reference standard, mg; S is strength of the reference standard, decimal; V1 is the volume of dissolution medium used to dissolve the dosage form, mL; 0.884 is the percent free base, Ar is the absorbance of the standard preparation, V2 is the volume of reference standard solution, mL; and C is the capsule claim in mg.

Table 2 shows the plasma level of venlafaxine versus time for one 75 mg conventional Immediate Release (IR) tablet administered every 12 hours, two 75 mg extended release (ER) capsules administered simultaneously every 24 hours, and one 150 mg extended release (ER) capsule administered once every 24 hours in human male subjects. The subjects were already receiving venlafaxine hydrochloride according to the dosage protocol, thus the plasma blood level at zero time when dosages were administered is not zero.

TABLE 2

Plasma venlafaxine level (ng/mL) versus time, conventional tablet (not extended release) versus ER causule

Time (hours)	75 mg (IR) tablet (q 12 h)	2 × 75 mg (ER) capsules (q 24 hr)	1 × 150 mg (ER) capsules (q 24 h)
0	62.3	55.0	55.8
0.5	76.3		
1	135.6	53.3	53.2
2	212.1	69.8	70.9
4	162.0	138.6	133.3
6	114.6	149.0	143.5
8	86.7	129.3	129.5
10		118.4	114.4
12	51.9	105.1	105.8
12.5	74.7		
13	127.5		
14	161.3	90.5	91.3
16	134.6	78.2	78.5
18	106.2		
20	83.6	62.7	63.3
24	57.6	56.0	57.3

Table 2 shows that the plasma levels of two 75 mg/capsule venlafaxine hydrochloride ER capsules and one 150 mg/capsule venlafaxine hydrochloride ER capsule provide very similar blood levels. The data also show that the plasma level after 24 hours for either extended release regimen is very similar to that provided by two immediate release 75 mg tablets of venlafaxine hydrochloride administered at 12 hour intervals.

Further, the plasma levels of venlafaxine obtained with the extended release formulation do not increase to the peak levels obtained with the conventional immediate release tablets given 12 hours apart. The peak level of venlafaxine from (ER), somewhat below 150 ng/ml, is reached in about six hours, plus or minus two hours, based upon this specific dose when administered to patients presently under treatment with venlafaxine hydrochloride (IR). The peak plasma level of venlafaxine, somewhat over 200 ng/ml, following administration of (IR) is reached in two hours and falls rapidly thereafter.

Table 3 shows venlafaxine blood plasma levels in male human subjects having a zero initial blood plasma level. Again, a peak blood plasma concentration of venlafaxine is seen at about 6 hours after dosing with venlafaxine hydrochloride extended release capsules in the quantities indicated The subjects receiving the single 50 mg immediate release tablet showed a peak plasma level occurring at about 4 hours. For comparative purposes, the plasma levels of venlafaxine for subjects receiving the conventional formulated tablet can be multiplied by a factor of three to approximate the plasma levels expected for a single dose of 150 mg. conventional formulation.

TABLE 3

Plasma Blood Levels in Human Males Having No Prior Venlafaxine Blood Level

Time (Hours)	1 × 50 mg IR tablet	2 × 75 mg ER capsules	1 × 150 mg ER capsule
0	0	0	0
1	27.87	1.3	0
1.5	44.12	6.0	2.2
2	54.83	20.6	12.8
4	66.38	77.0	81.0
6	49.36	96.5	94.4
8	30.06	93.3	86.9
10	21.84	73.2	72.8
12	15.91	61.3	61.4
14	13.73	52.9	51.9
16	10.67	47.5	41.1
20	5.52	35.2	34.0
24	3.56	29.3	28.5
28	2.53	23.4	22.9
36	1.44	11.9	13.5
48	0.66	5.8	5.2

The blood plasma levels of venlafaxine were measured according to the following procedure. Blood samples from the subjects were collected in heparinized evacuated blood tubes and the tubes were inverted gently several times. As quickly as possible, the tubes were centrifuged at 2500 rpm for 15 minutes. The plasma was pipetted into plastic tubes and stored at −20° C. until analysis could be completed.

To 1 mL of each plasma sample in a plastic tube was added 150 μL of a stock internal standard solution (150 μg/ml). Saturated sodium borate (0.2 mL) solution was added to each tube and vortexed. Five mL of ethyl ether was added to each tube which were then capped and shaken for 10 minutes at high speed. The tubes were centrifuged at 3000 rpm for 5 minutes. The aqueous layer was frozen in dry ice and the organic layer transferred to a clean screw cap tube. A 0.3 ml portion of 0.01 N HCl solution was added to each tube and shaken for 10 minutes at high speed. The aqueous layer was frozen and the organic layer removed and discarded. A 50 μL portion of the mobile phase (23:77 acetonitrile:0.1M monobasic ammonium phosphate buffer, pH 4.4) was added to each tube, vortexed, and 50 μL samples were injected on a Superco Supercoil LC-8-DB, 5 cm×4.6 mm, 5 μ column in a high pressure liquid chromatography apparatus equipped with a Waters Lambda Max 481 detector or equivalent at 229 nm. Solutions of venlafaxine hydrochloride at various concentrations were used as standards.

EXAMPLE NO. 5

Manufactured by the techniques described herein, another preferred formulation of this invention comprises spheroids of from about 30% to about 35% venlafaxine hydrochloride and from about 0.3% to about 0.6% hydroxypropylmethylcellulose. These spheroids are then coated with a film coating, as described above, to a coating level of from about 5% to about 9%, preferably from about 6% to about 8%. A specific formulation of this type comprises spheroids of about 33% venlafaxine hydrochloride and about 0.5% hydroxypropylmethylcellulose, with a film coating of about 7%.

Lower dosage compositions or formulations of this invention may also be produced by the techniques described herein. These lower dosage forms may be administered alone for initial titration or initiation of treatment, prior to a dosage increase. They may also be used for an overall low-dose administration regimen or in combination with higher dosage compositions, such as capsule formulations, to optimize individual dosage regimens.

These lower dose compositions may be used to create encapsulated formulations, such as those containing doses of venlafaxine hydrochloride from about 5 mg to about 50 mg per capsule. Particular final encapsulated dosage forms may include, but are not limited to, individual doses of 7.5 mg, 12.5 mg, 18.75 mg, or 28.125 mg of venlafaxine HCl per capsule.

The spheroids useful in these lower dose formulations may comprise from about 5% to about 29.99% venlafaxine HCl, preferably from about 5% to about 25%, from about 75% to about 95% microcrystalline cellulose, and, optionally from about 0.25% to about 1.0% hydroxypropylmethylcellulose. The spheroids may be coated as described above, preferably with a film coating of from about 5% to about 10% by weight. In some preferred formulations, the spheroids comprise the cited venlafaxine HCl and microcrystalline cellulose, with no hydroxypropylmethyl cellulose.

EXAMPLE NO. 6

Spheroids comprising 16.5% venlafaxine HCl and 83.5% microcrystalline cellulose were mixed with approximately 50% water (w/w) to granulate in a Littleford Blender Model FM-50E/1Z (Littleford Day Inc., P.O. Box 128, Florence, Kent. 41022-0218, U.S.A.) at a fixed speed of 180 rpm. The blended material was extruded through a 1.25 mm screen using a Nica extruder/spheronization machine (Aeromatic-Fielder Division, Niro Inc., 9165 Rumsey Rd., Columbia, Md. 21045, U.S.A.) for a 12/20 mesh cut after drying. Two portions of the resulting spheroids were coated with a 5% and 7% coating level, respectively, by techniques described above using the coating formulation:

Ingredient	% (w/w)
Methylene Chloride	60.000
Methanol Anhydrous	35.500
Ethylcellulose, NF, HG 2834, 50 cps	3.825
Hydroxypropyl Methylcelluose, 2910 USP, 6 cps	0.675

The 5% and 7% coated lots were tested for dissolution on a Hewlett Packard automated dissolution system over a 24 hour period, resulting in the following dissolution patterns:

Time/hr	% Dissoluded 16.5%/5%	% Dissolved 16.5%/7%
2	12.4	5.6
4	42.8	25.4
8	70.7	60.4
12	82.2	75.4
24	94.3	92.7

EXAMPLE NO. 7

A formulation of spheroids containing 8.25% venlafaxine HCl and 91.75% microcrystalline cellulose was prepared according to the techniques of Example No. 6 and coated with a 5% film coating. In the Hewlett Packard automated dissolution system these spheroids provided the following dissolution profile:

Time/hr	% Dissolved 8.25%/5%
2	4.4
4	24.2
8	62.9
12	77.8
24	93.5

Thus, the desired dissolution rates of sustained release dosage forms of venlafaxine hydrochloride, impossible to achieve with hydrogel tablet technology, has been achieved with the film-coated spheroid compositions of this invention.

What is claimed is:

1. A method for providing therapeutic blood plasma concentration of venlafaxine over a twenty four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof, an extended release formulation that provides peak blood plasma levels of venlafaxine of no more than about 150 ng/ml, said formulation containing venlafaxine hydrochloride as the active ingredient.

2. The method of claim 1 wherein the extended release formulation is encapsulated.

3. The method of claim 1 wherein the extended release formulation comprises venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and optionally, hydroxypropylmethylcellulose.

4. The method of claim 3 wherein the spheroids are comprised of from about 6% to about 40% venlafaxine hydrochloride by weight, about 50% to about 94% microcrystalline cellulose by weight, and optionally from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

5. The method of claim 3 wherein the spheroids are coated with from about 2% to about 12% of total formulation weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

6. The method of claim 5 wherein the spheroids are comprised of about 30% to 40% venlafaxine hydrochloride by weight, about 50% to about 70% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP.

7. The method of claim 6 wherein the spheroids are coated with from about 2% to about 12% of total formulation weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

8. The method of claim 3 wherein the spheroids are coated with from about 6% to about 30% venlafaxine hydrochloride by weight, about 70.1 % to about 94% microcrystalline cellulose, NF, by weight and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

9. The method of claim 8 wherein the spheroids are coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

10. The method of claim 3 wherein the spheroids are coated with from about 5% to about 25% venlafaxine hydrochloride and from about 95% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

11. The method of claim 3 wherein the spheroids are coated with from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

12. The method of claim 11 wherein the spheroids are comprised of about 6% to about 20% venlafaxine hydrochloride and from about 94% to about 80% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

13. The method of claim 1 wherein the extended release formulation comprising venlafaxine hydrochloride in a spheroid.

14. The method of claim 1 wherein the extended release formulation comprises venlafaxine hydrochloride in an encapsulated spheroid.

* * * * *

Exhibit 34

US006419958B2

(12) **United States Patent**
Sherman et al.

(10) **Patent No.: US 6,419,958 B2**
(45) **Date of Patent: *Jul. 16, 2002**

(54) **EXTENDED RELEASE FORMULATION OF VENLAFAXINE HYDROCHLORIDE**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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Related U.S. Application Data

(60) Division of application No. 09/488,629, filed on Jan. 20, 2000, now Pat. No. 6,274,171, which is a continuation-in-part of application No. 08/964,328, filed on Nov. 5, 1997, now abandoned, which is a continuation-in-part of application No. 08/821,137, filed on Mar. 20, 1997, now abandoned.

(60) Provisional application No. 60/014,006, filed on Mar. 25, 1996.

(51) **Int. Cl.**[7] **A61K 9/14**

(52) **U.S. Cl.** **424/489**; 424/457

(58) **Field of Search** 424/495, 494, 424/461, 458, 459, 457, 456, 462, 489

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(57) **ABSTRACT**

This invention relates to a 24 hour extended release dosage formulation and unit dosage form thereof of venlafaxine hydrochloride, an antidepressant, which provides better control of blood plasma levels than conventional tablet formulations which must be administered two or more times a day and further provides a lower incidence of nausea and vomiting than the conventional tablets. More particularly, the invention comprises an extended release formulation of venlafaxine hydrochloride comprising a therapeutically effective amount of venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and, optionally, hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose.

6 Claims, No Drawings

EXTENDED RELEASE FORMULATION OF VENLAFAXINE HYDROCHLORIDE

This application is a divisional application of Ser. No. 09/488,629, filed Jan. 20, 2000 U.S. Pat. No. 6,274,171 which is a continuation-in-part of application Ser. No. 08/964,328, filed Nov. 5, 1997, now abandoned, which is a continuation-in-part of application Ser. No. 08/821,137, filed Mar. 20, 1997, now abandoned, which claims priority from Provisional Application No. 60/014,006 filed Mar. 25, 1996.

BACKGROUND OF THE INVENTION

Extended release drug formulations are conventionally produced as compressed tablets by hydrogel tablet technology. To produce these sustained release tablet drug dosage forms, the active ingredient is conventionally compounded with cellulose ethers such as methyl cellulose, ethyl cellulose or hydroxypropylmethylcellulose with or without other excipients and the resulting mixture is pressed into tablets. When the tablets are orally administered, the cellulose ethers in the tablets swell upon hydration from moisture in the digestive system, thereby limiting exposure of the active ingredient to moisture. As the cellulose ethers are gradually leached away by moisture, water more deeply penetrates the gel matrix and the active ingredient slowly dissolves and diffuses through the gel, making it available for absorption by the body. An example of such a sustained release dosage form of the analgesic/anti-inflammatory drug etodolac (Lodine®) appears in U.S. Pat. No. 4,966,768. U.S. Pat. No. 4,389,393 discloses sustained release therapeutic compressed solid unit dose forms of an active ingredient plus a carrier base comprised of a high molecular weight hydroxypropylmethylcellulose, methyl cellulose, sodium carboxymethylcellulose and or other cellulose ether.

Where the production of tablets is not feasible, it is conventional in the drug industry to prepare encapsulated drug formulations which provide extended or sustained release properties. In this situation, the extended release capsule dosage forms may be formulated by mixing the drug with one or more binding agents to form a uniform mixture which is then moistened with water or a solvent such as ethanol to form an extrudable plastic mass from which small diameter, typically 1 mm, cylinders of drug/matrix are extruded, broken into appropriate lengths and transformed into spheroids using standard spheronization equipment. The spheroids, after drying, may then be film-coated to retard dissolution. The film-coated spheroids may then be placed in pharmaceutically acceptable capsules, such as starch or gelatin capsules, in the quantity needed to obtain the desired therapeutic effect. Spheroids releasing the drug at different rates may be combined in a capsule to obtain desired release rates and blood levels. U.S. Pat. No. 4,138,475 discloses a sustained release pharmaceutical composition consisting of a hard gelatin capsule filled with film-coated spheroids comprised of propanolol in admixture with microcrystalline cellulose wherein the film coating is composed of ethyl cellulose, optionally, with hydroxypropylmethylcellulose and/or a plasticizer.

Venlafaxine, 1-[2-(dimethylamino)-1-(4-methoxyphenyl) ethyl]cyclohexanol, is an important drug in the neuropharmacological arsenal used for treatment of depression. Venlafaxine and the acid addition salts thereof are disclosed in U.S. Pat. No. 4,535,186. Venlafaxine hydrochloride is presently administered to adults in compressed tablet form in doses ranging from 75 to 350 mg/day, in divided doses two or three times a day. In therapeutic dosing with venlafaxine hydrochloride tablets, rapid dissolution results in a rapid increase in blood plasma levels of the active compound shortly after administration followed by a decrease in blood plasma levels over several hours as the active compound is eliminated or metabolized, until sub-therapeutic plasma levels are approached after about twelve hours following administration, thus requiring additional dosing with the drug. With the plural daily dosing regimen, the most common side effect is nausea, experienced by about forty five percent of patients under treatment with venlafaxine hydrochloride. Vomiting also occurs in about seventeen percent of the patients.

BRIEF DESCRIPTION OF THE INVENTION

In accordance with this invention, there is provided an extended release (ER), encapsulated formulation containing venlafaxine hydrochloride as the active drug component, which provides in a single dose, a therapeutic blood serum level over a twenty four hour period.

Through administration of the venlafaxine formulation of this invention, there is provided a method for obtaining a flattened drug plasma concentration to time profile, thereby affording a tighter plasma therapeutic range control than can be obtained with multiple daily dosing. In other words, this invention provides a method for eliminating the sharp peaks and troughs (hills and valleys) in blood plasma drug levels induced by multiple daily dosing with conventional immediate release venlafaxine hydrochloride tablets. In essence, the plasma levels of venlafaxine hydrochloride rise, after administration of the extended release formulations of this invention, for between about five to about eight hours (optimally about six hours) and then begin to fall through a protracted, substantially linear decrease from the peak plasma level for the remainder of the twenty four hour period, maintaining at least a threshold therapeutic level of the drug during the entire twenty-four period. In contrast, the conventional immediate release venlafaxine hydrochloride tablets give peak blood plasma levels in 2 to 4 hours. Hence, in accordance with the use aspect of this invention, there is provided a method for moderating the plural blood plasma peaks and valleys attending the pharmacokinetic utilization of multiple daily tablet dosing with venlafaxine hydrochloride which comprises administering to a patient in need of treatment with venlafaxine hydrochloride, a one-a-day, extended release formulation of venlafaxine hydrochloride.

The use of the one-a-day venlafaxine hydrochloride formulations of this invention reduces by adaptation, the level of nausea and incidence of emesis that attend the administration of multiple daily dosing. In clinical trials of venlafaxine hydrochloride ER, the probability of developing nausea in the course of the trials was greatly reduced after the first week. Venlafaxine ER showed a statistically significant improvement over conventional venlafaxine hydrochloride tablets in two eight-week and one 12 week clinical studies. Thus, in accordance with this use aspect of the invention there is provided a method for reducing the level of nausea and incidence of emesis attending the administration of venlafaxine hydrochloride which comprises dosing a patient in need of treatment with venlafaxine hydrochloride with an extended release formulation of venlafaxine hydrochloride once a day in a therapeutically effective amount.

The formulations of this invention comprise an extended release formulation of venlafaxine hydrochloride comprising a therapeutically effective amount of venlafaxine hydro-

chloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and, optionally, hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose. Unless otherwise noted, the percentage compositions mentioned herein refer to percentages of the total weight of the final composition or formulation.

More particularly, the extended release formulations of this invention are those above wherein the spheroids are comprised of from about 6% to about 40% venlafaxine hydrochloride by weight, about 50% to about 95% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

A preferred embodiment of this invention are formulations wherein the spheroids are comprised of about 30% to about 40% venlafaxine hydrochloride by weight, about 50% to about 70% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

Another preferred lower dose formulation of this invention are those wherein the spheroids are comprised less than 30% venlafaxine hydrochloride. These formulations comprise spheroids of from about 6% to about 30% venlafaxine hydrochloride by weight, about 70% to about 94% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

Within this subgroup of lower dose formulations are formulations in which the spheroids are comprised of from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. Another preferred subgroup of spheroids in these formulations comprises from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. A further preferred subgroup of spheroids in these formulations comprises from about 6% to about 20% venlafaxine hydrochloride and from about 94% to about 80% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. Within each of these subgroups is understood to be formulations in which the spheroids are comprised of venlafaxine HCl and microcrystalline cellulose in the amounts indicated, with no hydroxypropylmethylcellulose present. Each of these formulations is also preferably contained in a gelatin capsule, preferably a hard gelatin capsule.

DETAILED DESCRIPTION OF THE INVENTION

1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride is polymorphic. Of the forms isolated and characterized to date, Form I is considered to be the kinetic product of crystallization which can be converted to Form II upon heating in the crystallization solvent. Forms I and II cannot be distinguished by their melting points but do exhibit some differences in their infrared spectra and X-ray diffraction patterns. Any of the polymorphic forms such as Form I or Form II may be used in the formulations of the present invention.

The extended release formulations of this invention are comprised of 1-[2-(dimethylamino)-1-(4-methoxyphenyl) ethyl] cyclohexanol hydrochloride in admixture with microcrystalline cellulose and hydroxypropylmethylcellulose. Formed as beads or spheroids, the drug containing formulation is coated with a mixture of ethyl cellulose and hydroxypropylmethyl cellulose to provide the desired level of coating, generally from about two to about twelve percent on a weight/weight basis of final product or more preferably from about five to about ten percent (w/w), with best results obtained at from about 6 to about 8 percent (w/w). More specifically, the extended release spheroid formulations of this invention comprise from about 30 to 40 percent venlafaxine hydrochloride, from about 50 to about 70 percent microcrystalline cellulose, NF, from about 0.25 to about 1 percent hydroxypropylmethylcellulose, USP, and from about 5 to about 10 percent film coating, all on a weight/weight basis. And preferably, the spheroid formulations contain about 35 percent venlafaxine hydrochloride, about 55 to 60 percent microcrystalline cellulose NF (Avicel® PH101), about one half percent hydroxypropylmethylcellulose 2208 USP (K3, Dow, which has a viscosity of 3 cps for 2% aqueous solutions, a methoxy content of 19–24% and a hydroxypropoxy content of 4–13%), and from about 6 to 8 percent film coating.

The film coating is comprised of 80 to 90 percent of ethyl cellulose, NF and 10 to 20 percent hydroxypropylmethylcellulose (2910), USP on a weight/weight basis. Preferably the ethyl cellulose has a ethoxy content of 44.0–51% and a viscosity of 50 cps for a 5% aqueous solution and the hydroxypropylrnethylcellulose is USP 2910 having a viscosity of 6 cps at 2% aqueous solution with a methoxy content of 28–30% and a hydroxypropoxy content of 7–12%. The ethyl cellulose used herein is Aqualon HG 2834.

Other equivalents of the hydroxypropylmethylcelluloses 2208 and 2910 USP and ethyl cellulose, NF, having the same chemical and physical characteristics as the proprietary products named above may be substituted in the formulation without changing the inventive concept. Important characteristics of suitable hydroxypropylmethylcelluloses include a low viscosity, preferably less than 10 cps and more preferably 2–5 cps, and a gel temperature above that of the temperature of the extrudate during extrusion. As explained below, these and other characteristics which enable the extrudate to remain moist and soft (pliable) are preferred for the hydroxypropylmethylcellulose. In the examples below, the extrudate temperature was generally 50–55° C.

It was completely unexpected that an extended release formulation containing venlafaxine hydrochloride could be obtained because the hydrochloride of venlafaxine proved to be extremely water soluble. Numerous attempts to produce extended release tablets by hydrogel technology proved to be fruitless because the compressed tablets were either physically unstable (poor compressibility or capping problems) or dissolved too rapidly in dissolution studies. Typically, the tablets prepared as hydrogel sustained release formulations gave 40–50% dissolution at 2 hrs, 60–70% dissolution at 4 hrs and 85–100% dissolution at 8 hrs.

Numerous spheroid formulations were prepared using different grades of microcrystalline cellulose and hydroxypropylmethylcellulose, different ratios of venlafaxine hydrochloride and filler, different binders such as polyvinylpyrrolidone, methylcellulose, water, and polyethylene glycol of different molecular weight ranges in order to find a formulation which would provide a suitable granulation mix which could be extruded properly. In the extrusion process, heat buildup occurred which dried out the extrudate so much that it was difficult to convert the extruded cylinders into spheroids. Addition of hydroxypropylmethylcellulose 2208 to the venlafaxine hydrochloride-microcrystalline cellulose mix made production of spheroids practical.

The encapsulated formulations of this invention may be produced in a uniform dosage for a specified dissolution profile upon oral administration by techniques understood in the art. For instance, the spheroid components may be blended for uniformity with a desired concentration of active ingredient, then spheronized and dried. The resulting spheroids can then be sifted through a mesh of appropriate pore size to obtain a spheroid batch of uniform and prescribed size.

The resulting spheroids can be coated and resifted to remove any agglomerates produced in the coating steps. During the coating process samples of the coated spheroids may be tested for their distribution profile. If the dissolution occurs too rapidly, additional coating may be applied until the spheroids present a desired dissolution rate.

The following examples are presented to illustrate applicant's solution to the problem of preparation of the extended release drug containing formulations of this invention.

EXAMPLE NO. 1

Venlafaxine Hydrochloride Extended Release Capsules

A mixture of 44.8 parts (88.4% free base) of venlafaxine hydrochloride, 74.6 parts of the microcrystalline cellulose, NF, and 0.60 parts of hydroxypropylmethyl cellulose 2208, USP, are blended with the addition of 41.0 parts water. The plastic mass of material is extruded, spheronized and dried to provide uncoated drug containing spheroids.

Stir 38.25 parts of ethyl cellulose, NF, HG2834 and 6.75 parts of hydroxypropylmethylcellulose 2910, USP in a 1:1 v/v mixture of methylene chloride and anhydrous methanol until solution of the film coating material is complete.

To a fluidized bed of the uncoated spheroids is applied 0.667 parts of coating solution per part of uncoated spheroids to obtain extended release, film coated spheroids having a coating level of 3%.

The spheroids are sieved to retain the coated spheroids of a particle size between 0.85 mm to 1.76 mm diameter. These selected film coated spheroids are filled into pharmaceutically acceptable capsules conventionally, such as starch or gelatin capsules.

EXAMPLE NO. 2

Same as for Example 1 except that 1.11 parts of the film coating solution per part of uncoated spheroids is applied to obtain a coating level of 5%.

EXAMPLE NO. 3

Same as for Example 1 except that 1.33 parts of the film coating solution is applied to 1 part of uncoated spheroids to obtain a coating level of 6%.

EXAMPLE NO. 4

Same as for Example 1 except that 1.55 parts of the film coating solution is applied to 1 part of uncoated spheroids to obtain a coating level of 7%.

In the foregoing failed experiments and in Examples 1–4, the extrusion was carried out on an Alexanderwerk extruder. Subsequent experiments carried out on Hutt and Nica extruders surprisingly demonstrated that acceptable, and even improved, spheroids could be made without the use of an hydroxypropylmethylcellulose.

In such further experiments the applicability of the invention was extended to formulations wherein the weight percentage of venlafaxine hydrochloride is 6% to 40%, preferably 8% to 35%. Thus, the extended release spheroid formulations of this invention comprise from about 6 to about 40 percent venlafaxine hydrochloride, from about 50 to about 94 percent microcrystalline cellulose, NF, optionally, from about 0.25 to about 1 percent hydroxypropylmethylcellulose, and from about 2 to about 12 percent, preferably about 3 to 9 percent, film coating.

Spheroids of the invention were produced having 8.25% (w/w) venlafaxine hydrochloride and the remainder (91.75%, w/w) being microcrystalline cellulose, with a coating of from 3 to 5% (w/w), preferably 4%, of the total weight. The spheroids with 8.25% venlafaxine hydrochloride and 4% coating were filled into No. 2 white opaque shells with a target fill weight of 236 mg.

Further spheroids of the invention were produced having 16.5% (w/w) venlafaxine hydrochloride and the remainder (83.5%, w/w) being microcrystalline cellulose, with a coating of from 4 to 6% (w/w), preferably 5%, of the total weight. The spheroids 16.5% venlafaxine hydrochloride and 5% coating were filled into No. 2 white opaque shells with a target fill weight of 122 mg.

The test for acceptability of the coating level is determined by analysis of the dissolution rate of the finished coated spheroids prior the encapsulation. The dissolution procedure followed uses USP Apparatus 1 (basket) at 100 rpm in purified water at 37° C.

Conformance with the dissolution rate given in Table 1 provides the twenty-four hour therapeutic blood levels for the drug component of the extended release capsules of this invention in capsule form. Where a given batch of coated spheroids relases drug too slowly to comply with the desired dissolution rate study, a portion of uncoated spheroids or spheroids with a lower coating level may be added to the batch to provide, after thorough mixing, a loading dose for rapid increase of blood drug level. A batch of coated spheroids that releases the drug too rapidly can receive additional film-coating to give the desired dissolution profile.

TABLE 1

Acceptable Coated Spheroid Dissolution Rates

Time (hours)	Average % Venlafaxine HCl released
2	<30
4	30–55
8	55–80
12	65–90
24	>80

Batches of the coated venlafaxine hydrochloride containing spheroids which have a dissolution rate corresponding to

that of Table 1 are filled into pharmaceutically acceptable capsules in an amount needed to provide the unit dosage level desired. The standard unit dosage immediate release (IR) tablet used presently provides amounts of venlafaxine hydrochloride equivalent to 25 mg, 37.5 mg, 50 mg, 75 mg and 100 mg venlafaxine. The capsules of this invention are filled to provide an amount of venlafaxine hydrochloride equivalent to that presently used in tablet form and also up to about 150 mg venlafaxine hydrochloride.

Dissolution of the venlafaxine hydrochloride ER capsules is determined as directed in the U.S. Pharmacopoeia (USP) using apparatus 1 at 100 rpm on 0.9 L of water. A filtered sample of the dissolution medium is taken at the times specified. The absorbance of the clear solution is determined from 240 to 450 nanometers (nm) against the dissolution medium. A baseline is drawn from 450 nm through 400 nm and extended to 240 nm. The absorbance at the wavelength of maximum absorbance (about 274 nm) is determined with respect to this baseline. Six hard gelatin capsules are filled with the theoretical amount of venlafaxine hydrochloride spheroids and measured for dissolution. Standard samples consist of venlafaxine hydrochloride standard solutions plus a gelatin capsule correction solution.

The percentage of venlafaxine released is determined from the equation

$$\%\ Venlafaxine\ hydrochloride\ released = \frac{(As)(Wr)(S)(V1)(0.888)(100)}{(Ar)(V2)(C)}$$

where As is absorbance of sample preparation, Wr is weight of reference standard, mg; S is strength of the reference standard, decimal; V1 is the volume of dissolution medium used to dissolve the dosage form, mL; 0.884 is the percent free base, Ar is the absorbance of the standard preparation, V2 is the volume of reference standard solution, mL; and C is the capsule claim in mg.

Table 2 shows the plasma level of venlafaxine versus time for one 75 mg conventional Immediate Release (IR) tablet administered every 12 hours, two 75 mg extended release (ER) capsules administered simultaneously every 24 hours, and one 150 mg extended release (ER) capsule administered once every 24 hours in human male subjects. The subjects were already receiving venlafaxine hydrochloride according to the dosage protocol, thus the plasma blood level at zero time when dosages were administered is not zero.

TABLE 2

Plasma venlafaxine level (ng/mL) versus time, conventional tablet (not extended release) versus ER capsule

Time (hours)	75 mg (IR) tablet (q 12h)	2 × 75 mg (ER) capsules (q 24hr)	1 × 150 mg (ER) capsules (q 24h)
0	62.3	55.0	55.8
0.5	76.3		
1	135.6	53.3	53.2
2	212.1	69.8	70.9
4	162.0	138.6	133.3
6	114.6	149.0	143.5
8	86.7	129.3	129.5
10		118.4	114.4
12	51.9	105.1	105.8
12.5	74.7		
13	127.5		
14	161.3	90.5	91.3
16	134.6	78.2	78.5
18	106.2		
20	83.6	62.7	63.3
24	57.6	56.0	57.3

Table 2 shows that the plasma levels of two 75 mg/capsule venlafaxine hydrochloride ER capsules and one 150 mg/capsule venlafaxine hydrochloride ER capsule provide very similar blood levels. The data also show that the plasma level after 24 hours for either extended release regimen is very similar to that provided by two immediate release 75 mg tablets of venlafaxine hydrochloride administered at 12 hour intervals.

Further, the plasma levels of venlafaxine obtained with the extended release formulation do not increase to the peak levels obtained with the conventional immediate release tablets given 12 hours apart. The peak level of venlafaxine from (ER), somewhat below 150 ng/ml, is reached in about six hours, plus or minus two hours, based upon this specific dose when administered to patients presently under treatment with venlafaxine hydrochloride (IR). The peak plasma level of venlafaxine, somewhat over 200 ng/ml, following administration of (IR) is reached in two hours and falls rapidly thereafter.

Table 3 shows venlafaxine blood plasma levels in male human subjects having a zero initial blood plasma level. Again, a peak blood plasma concentration of venlafaxine is seen at about 6 hours after dosing with venlafaxine hydrochloride extended release capsules in the quantities indicated. The subjects receiving the single 50 mg immediate release tablet showed a peak plasma level occurring at about 4 hours. For comparative purposes, the plasma levels of venlafaxine for subjects receiving the conventional formulated tablet can be multiplied by a factor of three to approximate the plasma levels expected for a single dose of 150 mg. conventional formulation.

TABLE 3

Plasma Blood Levels in Human Males Having No Prior Venlafaxine Blood Level

Time (Hours)	1 × 50 mg IR tablet	2 × 75 mg ER capsules	1 × 150 mg ER capsules
0	0	0	0
1	27.87	1.3	0
1.5	44.12	6.0	2.2
2	54.83	20.6	12.8
4	66.38	77.0	81.0
6	49.36	96.5	94.4
8	30.06	93.3	86.9
10	21.84	73.2	72.8
12	15.91	61.3	61.4
14	13.73	52.9	51.9
16	10.67	47.5	41.1
20	5.52	35.2	34.0
24	3.56	29.3	28.5
28	2.53	23.4	22.9
36	1.44	11.9	13.5
48	0.66	5.8	5.2

The blood plasma levels of venlafaxine were measured according to the following procedure. Blood samples from

the subjects were collected in heparinized evacuated blood tubes and the tubes were inverted gently several times. As quickly as possible, the tubes were centrifuged at 2500 rpm for 15 minutes. The plasma was to plastic tubes and stored at −20° C. until analysis could be completed.

To 1 mL of each plasma sample in a plastic tube was added 150 μL of a stock internal standard solution (150 μg/ml). Saturated sodium borate (0.2 mL) solution was added to each tube and vortexed. Five mL of ethyl ether was added to each tube which were then capped and shaken for 10 minutes at high speed. The tubes were centrifuged at 3000 rpm for 5 minutes. The aqueous layer was frozen in dry ice and the organic layer transferred to a clean screw cap tube. A 0.3 mL portion of 0.01 N HCl solution was added to each tube and shaken for 10 minutes at high speed. The aqueous layer was frozen and the organic layer removed and discarded. A 50 μL portion of the mobile phase (23:77 acetonitrile:0.1M monobasic ammonium phosphate buffer, pH 4.4) was added to each tube, vortexed, and 50 μL samples were injected on a Supelco Supelcoil LC-8-DB, 5 cm×4.6 mm, 5 μ column in a high pressure liquid chromatography apparatus equipped with a Waters Lambda Max 481 detector or equivalent at 229 nm. Solutions of venlafaxine hydrochloride at various concentrations were used as standards.

EXAMPLE NO. 5

Manufactured by the techniques described herein, another preferred formulation of this invention comprises spheroids of from about 30% to about 35% venlafaxine hydrochloride and from about 0.3% to about 0.6% hydroxypropylmethylcellulose. These spheroids are then coated with a film coating, as described above, to a coating level of from about 5% to about 9%, preferably from about 6% to about 8%. A specific formulation of this type comprises spheroids of about 33% venlafaxine hydrochloride and about 0.5% hydroxypropylmethylcellulose, with a film coating of about 7%.

Lower dosage compositions or formulations of this invention may also be produced by the techniques described herein. These lower dosage forms may be administered alone for initial titration or initiation of treatment, prior to a dosage increase. They may also be used for an overall low-dose administration regimen or in combination with higher dosage compositions, such as capsule formulations, to optimize individual dosage regimens.

These lower dose compositions may be used to create encapsulated formulations, such as those containing doses of venlafaxine hydrochloride from about 5 mg to about 50 mg per capsule. Particular final encapsulated dosage forms may include, but are not limited to, individual doses of 7.5 mg, 12.5 mg, 18.75 mg, or 28.125 mg of venlafaxine HCl per capsule.

The spheroids useful in these lower dose formulations may comprise from about 5% to about 29.99% venlafaxine HCl, preferably from about 5% to about 25%, from about 75% to about 95% microcrystalline cellulose, and, optionally from about 0.25% to about 1.0% hydroxypropylmethylcellulose. The spheroids may be coated as described above, preferably with a film coating of from about 5% to about 10% by weight. In some preferred formulations, the spheroids comprise the cited venlafaxine HCl and microcrystalline cellulose, with no hydroxypropylmethyl cellulose.

EXAMPLE NO. 6

Spheroids comprising 16.5% venlafaxine HCl and 83.5% microcrystalline cellulose were mixed with approximately 50% water (w/w) to granulate in a Littleford Blender Model FM-50E/1Z (Littleford Day Inc., P.O. Box 128, Florence, Ky. 41022-0218, U.S.A.) at a fixed speed of 180 rpm. The blended. material was extruded through a 1.25 mm screen using a Nica extruder/speronization machine (Aeromatic-Fielder Division, Niro Inc., 9165 Rumsey Rd., Columbia, Md. 21045, U.S.A.) for a 12/20 mesh cut after drying. Two portions of the resulting spheroids were coated with a 5% and 7% coating level, respectively, by techniques described above using the coating formulation:

Ingredient	% (w/w)
Methylene Chloride	60.000
Methanol Anhydrous	35.500
Ethylcellulose, NF, HG 2834, 50 cps	3.825
Hydroxypropyl Methylcellulose, 2910 USP, 6 cps	0.675

These 5% and 7% coated lots were tested for dissolution on a Hewlett Packard automated dissolution system over a 24 hour period, resulting in the following dissolution patterns:

Time/hr	% Dissoluded 16.5%/5%	% Dissolved 16.5%/7%
2	12.4	5.6
4	42.8	25.4
8	70.7	60.4
12	82.2	75.4
24	94.3	92.7

A formulation of spheroids containing 8.25% venlafaxine HCl and 91.75% microcrystalline cellulose was prepared according to the techniques of Example No. 6 and coated with a 5% film coating. In the Hewlett Packard automated dissolution system these spheroids provided the following dissolution profile:

Time/hr	% Dissolved 8.25%/5%
2	4.4
4	24.2
8	62.9
12	77.8
24	93.5

Thus, the desired dissolution rates of sustained release dosage forms of venlafaxine hydrochloride, impossible to achieve with hydrogel tablet technology, has been achieved with the film-coated spheroid compositions of this invention.

What is claimed is:

1. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty-four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof, an extended release formulation that a peak blood plasma level of venlafaxine in from about 4 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

2. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine

hydrochloride which comprises administering orally to a patient in need thereof, extended release formulation that provides a peak blood plasma level of venlafaxine in from about 4 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

3. A method for providing a therapeutic drug plasma concentration of venlafaxine over a twenty-four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof, an extended release formulation that provides a peak blood plasma level of venlafaxine in from about 5 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

4. A method for providing a therapeutic drug plasma concentration of venlafaxine over a twenty-four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof, an extended release formulation that provides a peak blood plasma level of venlafaxine in about 6 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

5. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an extended release formulation that provides a peak blood plasma level of venlafaxine in from about 5 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

6. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an extended release formulation that provides a peak blood plasma level of venlafaxine in about 6 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

* * * * *

Exhibit 35

PW 1006160

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

May 15, 2003

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF THE FILE WRAPPER AND CONTENTS OF:

APPLICATION NUMBER: *08/821,137*
FILING DATE: *March 20, 1997*

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

H. Phillips
H. PHILLIPS
Certifying Officer

WYETH 002-000790

What is claimed is:

1. An encapsulated, extended release formulation of venlafaxine hydrochloride comprising a hard gelatin capsule containing a therapeutically effective amount of spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and hydroxypropyl methylcellulose coated with ethyl cellulose and hydroxypropylmethylcellulose.

2. An extended release formulation according to claim 1 wherein the spheroids are composed of about 37.3% by weight of venlafaxine hydrochloride, about 0.5% by weight of hydroxypropylmethylcellulose 2208, and about 62.17% by weight of microcrystalline cellulose.

3. A composition according to claim 1 wherein the film coating is comprised of ethyl cellulose (4.81% of total weight) and hydroxypropylmethylcellulose (0.85% of total weight).

4. A composition according to claim 1 wherein the film coating is comprised of ethyl cellulose (4.04% of total weight) and hydroxypropylmethylcellulose (0.714% of total weight).

5. A composition according to claim 1 wherein the film coating is comprised of ethyl cellulose (2.48% of total weight) and hydroxypropylmethylcellulose (0.437% of total weight).

6 A film coating composition which is composed of ethyl cellulose (15% of total weight), having a 44.0-51.0% content of ethoxy groups, and hydroxypropylmethylcellulose (85% of total weight) having a methoxy content of 28.0-30.0% and a hydroxypropoxy group content of 7.0-12.0%.

7. An extended release formulation of venlafaxine hydrochloride for once daily administration which comprises spheroids containing 37.3% venlafaxine, 62.17% microcrystalline cellulose and 0.5% hydroxypropylmethylcellulose type 2208, coated with a quantity of a mixture comprised of 15% ethyl cellulose type HG 2834 and 85% hydroxypropyl-methylcellulose type 2910 sufficient to give coated spheroids having a dissolution profile which gives the desired release rate over a 24 hour period.

7 8. An extended release formulation of venlafaxine hydrochloride according to claim 6 which provides lower peak serum levels of up to 150 ng/ml and extended therapeutically effective plasma levels over a twenty four hour period.

8 9. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty four hour period with diminished incidences of nausea and emesis which comprises administering orally to a patient in need thereof, the encapsulated, extended release formulation of claim 1 which provides a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

9 10. A method for eliminating the troughs and peaks of drug concentration in a patients blood plasma attending the therapeutic metabolism of plural daily doses of which comprises administering orally to a patient in need thereof, the encapsulated, extended release formulation of claim 1 which provides a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/821,137	03/20/97	SHERMAN D	AHP-95011

15M2/0805

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EXAMINER	
HULINA, A	
ART UNIT	PAPER NUMBER
1501	8

DATE MAILED: 08/05/97

INTERVIEW SUMMARY

All participants (applicant, applicant's representative, PTO personnel):

(1) Amy Hulina (3) _____

(2) Robert Boswell, Jr. (4) _____

Date of Interview 7/30/97

Type: ☒ Telephonic ☐ Personal (copy is given to ☐ applicant ☐ applicant's representative).

Exhibit shown or demonstration conducted: ☐ Yes ☒ No If yes, brief description: _____

Agreement ☒ was reached. ☐ was not reached.

Claim(s) discussed: 6, 9 and 10

Identification of prior art discussed: Upton et al. (5,506,270)

Description of the general nature of what was agreed to if an agreement was reached, or any other comments: Agreed to amend claims 9 and 10 to depend from claim 1 to avoid rejection over Upton which discloses extended release venlafaxine at col 5, lines 25-27

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendments which would render the claims allowable is available, a summary thereof must be attached.)

1. ☐ It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paragraph above has been checked to indicate to the contrary. A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a response to the last Office action has are ready been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW.

2. ☐ Since the Examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action. Applicant is not relieved from providing a separate record of the interview unless box 1 above is also checked.

Examiner Note: You must sign this form unless it is an attachment to another form.

FORM PTOL-413 (REV.1-96)

WYETH 002-000850

Manual of Patent Examining Procedure, Section 713.04 Substance of Interview must Be Made of Record

A complete written statement as to the substance of any face-to-face or telephone interview with regard to an application must be made of record in the application, whether or not an agreement with the examiner was reached at the interview.

§1.133 Interviews

* * * * *

(b) In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for response to Office action as specified in §§ 1.111,1.135. (35 U.S.C.132)

§ 1.2. Business to be transacted in writing. All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete a two-sheet carbon interleaf Interview Summary Form for each interview held after January 1, 1978 where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks in neat handwritten form using a ball point pen. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below.

The Interview Summary Form shall be given an appropriate paper number, placed in the right hand portion of the file, and listed on the "Contents" list on the file wrapper. The docket and serial register cards need not be updated to reflect interviews. In a personal interview, the duplicate copy of the Form is removed and given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephonic interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the telephonic interview rather than with the next official communication.

The Form provides for recordation of the following information:

- Serial Number of the application
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (personal or telephonic)
- Name of participant(s) (applicant, attorney or agent, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the claims discussed
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). (Agreements as to allowability are tentative and do not restrict further action by the examiner to the contrary.)
- The signature of the examiner who conducted the interview
- Names of other Patent and Trademark Office personnel present.

The Form also contains a statement reminding the applicant of his responsibility to record the substance of the interview.

It is desireable that the examiner orally remind the applicant of his obligation to record the substance of the interview in each case unless both applicant and examiner agree that the examiner will record same. Where the examiner agrees to record the substance of the interview, or when it is adequately recorded on the Form or in an attachment to the Form, the examiner should check a box at the bottom of the Form informing the applicant that he need not supplement the Form by submitting a separate record of the substance of the interview.

It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview:

A complete and proper recordation of the substance of any interview should include at least the following applicable items:

1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner. The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he feels were or might be persuasive to the examiner,
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Stimmary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete or accurate, the examiner will give the applicant one month from the date of the notifying letter or the remainder of any period for response, whichever is longer, to complete the response and thereby avoid abandonment of the application (37 CFR 1.135(c)).

Examiner to Check for Accuracy

Applicant's summary of what took place at the interview should be carefully checked to determine the accuracy of any argument or statement attributed to the examiner during the interview. If there is an inaccuracy and it bears directly on the question of patentability, it should be pointed out in the next Office letter. If the claims are allowable for other reasons of record, the examiner should send a letter setting forth his or her version of the statement attributed to him. If the record is complete and accurate, the examiner should place the indication "Interview record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

*U.S. GPO: 1998-404-498/40513

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: Box ISSUE FEE
ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

NOTICE OF ALLOWANCE AND ISSUE FEE DUE

1502/0805

RONALD W. ALICE
AMERICAN HOME PRODUCTS CORPORATION
ONE CAMPUS DRIVE
PARSIPPANY NJ 07054

APPLICATION NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT		DATE MAILED
08/821,137	03/20/97	009	HULINA, A	1501	08/05/97

First Named Applicant: SHERMAN, DEBORAH MARIE

TITLE OF INVENTION: EXTENDED RELEASE FORMULATION

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
AHP-95011	424-456.000	009	UTILITY	NO	$1290.00	11/05/97

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED.

THE ISSUE FEE MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED.

HOW TO RESPOND TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.
If the SMALL ENTITY is shown as yes, verify your current SMALL ENTITY status:

A. If the status is changed, pay twice the amount of the FEE DUE shown and notify the Patent and Trademark Office of the change in status, or
B. If the status is the same, pay the FEE DUE shown above.

If the SMALL ENTITY is shown as NO:

A. Pay FEE DUE shown above, or

B. File verified statementof Small Entity Status before, or with, payment of 1/2 the FEE DUE shown above.

II. Part B of this notice should be completed and returned to the Patent and Trademark Office (PTO) with your ISSUE FEE. Even if the ISSUE FEE has already been paid by charge to deposit account, Part B should be completed and returned. If you are charging the ISSUE FEE to your deposit account, section "6b" of Part B should be completed.

III. All communications regarding this application must give application number and batch number. Please direct all communication prior to issuance to Box ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

3. PATENT AND TRADEMARK OFFICE COPY

PTOL-85 (REV. 05-96)(0651-0033)

*U.S. GPO: 1996-404-496/40511

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address : COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/821,137	03/20/97	SHERMAN D	AHP-95011

75F1/0203

RONALD W. ALICE
AMERICAN HOME PRODUCTS CORPORATION
ONE CAMPUS DRIVE
PARSIPPANY NJ 07054

EXAMINER	
HULINA, A	
ART UNIT	PAPER NUMBER
1501	05

DATE MAILED: 02/03/98

NOTICE OF ABANDONMENT

This application is abandoned in view of:

1. ☐ Applicant's failure to respond to the Office letter, mailed _____ .
2. ☐ Applicant's letter of express abandonment which is in compliance with 37 C.F.R. 1.138.
3. ☐ Applicant's failure to timely file the response received _____ within the period set in the Office letter.
4. ☑ Applicant's failure to pay the required issue fee within the statutory period of 3 months from the mailing date of 08/05/97 of the Notice of Allowance.
   - ☐ The issue fee was received on _____ .
   - ☐ The issue fee has not been received in Allowed Files Branch as of _____ .

   In accordance with 35 U.S.C. 151, and under the provisions of 37 C.F.R. 1.316(b), applicant(s) may petition the Commissioner to accept the delayed payment of the issue fee if the delay in payment was unavoidable. The petition must be accompanied by the issue fee, unless it has been previously submitted, in the amount specified by 37 C.F.R. 1.17 (l), and a verified showing as to the causes of the delay.

   If applicant(s) never received the Notice of Allowance, a petition for a new Notice of Allowance and withdrawal of the holding of abandonment may be appropriate in view of Delgar Inc. v. Schuyler, 172 U.S.P.Q. 513.
5. ☐ Applicant's failure to timely correct the drawings and/or submit new or substitute formal drawings by _____ as required in the last Office action.
   - ☐ The corrected and/or substitute drawings were received on _____ .
6. ☐ The reason(s) below.

DIRECT ANY INQUIRIES TO :
PUBLISHING DIVISION
MARCIA CAMPBELL-JONES
(703) 305-8190
OR
PRISCILLA FULLER
(703) 305-8203

WYETH 002-000911

PTO-1432 (REV. 5-83)

Exhibit 36

PW 1006163

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

May 28, 2003

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF THE FILE WRAPPER AND CONTENTS OF:

APPLICATION NUMBER: ***08/964,328***
FILING DATE: ***November 05, 1997***

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

L. Edelen

L. EDELEN
Certifying Officer

WYETH 002-000563

What is claimed is:

1. An encapsulated, extended release formulation of venlafaxine hydrochloride comprising a hard gelatin capsule containing a therapeutically effective amount of venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and, optionally, hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose.

2. An extended release formulation according to claim 1 wherein the spheroids are comprised of about 30% to 40% venlafaxine hydrochloride by weight, about 50% to about 70% microcrystalline cellulose, NF, by weight, and from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

3. An encapsulated, extended release formulation of venlafaxine hydrochloride according to claim 1 having the following dissolution profile in USP Apparatus 1 (basket) at 100 rpm in purified water at 37°C:

Time (hours)	Average % Venlafaxine HCl released
2	<30
4	30-55
8	55-80
12	65-90
24	>80

4. An extended release formulation according to claim 2 wherein the spheroids are composed of about 37% by weight of venlafaxine hydrochloride, about 0.5% by weight of hydroxypropylmethylcellulose 2208, and about 62% by weight of microcrystalline cellulose.

5. A composition according to claim 2 wherein the film coating is comprised of ethyl cellulose (4.81% of total weight) and hydroxypropylmethylcellulose (0.85% of total weight).

6. A composition according to claim 2 wherein the film coating comprises 6- 8% by weight of total weight.

7. A composition according to claim 2 wherein the film coating is comprised of ethyl cellulose (2.48% of total weight) and hydroxypropylmethylcellulose (0.437% of total weight).

8. A composition according to claim 2 wherein film coating composition is comprised of ethyl cellulose having a 44.0-51.0% content of ethoxy groups and hydroxypropylmethylcellulose having a methoxy content of 28.0-30.0% and a hydroxypropoxy group content of 7.0-12.0%.

9. A film coating composition according to claim 7 which is comprised of about 85% by total weight of film coating of ethyl cellulose having a 44.0-51.0% content of ethoxy groups, and about 15% by total weight of film coating of hydroxypropylmethylcellulose having a methoxy content of 28.0-30.0% and a hydroxypropoxy group content of 7.0-12.0%.

10. A film coating composition according to claim 7 which is comprised of 85% by weight of ethyl cellulose type HG 2834 and 15% by weight of hydroxypropylmethylcellulose type 2910.

11. An extended release formulation of venlafaxine hydrochloride for once daily administration which comprises spheroids containing 37.3% venlafaxine, 62.17% microcrystalline cellulose and 0.5% hydroxypropylmethylcellulose type 2208, coated with a quantity of a mixture comprised of 85% ethyl cellulose type HG 2834 and 15% hydroxypropyl-methylcellulose type 2910 sufficient to give coated spheroids having a dissolution profile which gives the desired release rate over a 24 hour period.

12. An extended release formulation of venlafaxine hydrochloride according to claim 7 which provides peak serum levels of up to 150 ng/ml and extended therapeutically effective plasma levels over a twenty four hour period.

13. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty four hour period with diminished incidences of nausea and emesis which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

14. A method for eliminating the troughs and peaks of drug concentration in a patients blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

Sub A4

15. An extended release formulation according to claim 1 wherein the spheroids are comprised of about 6% to 40% venlafaxine hydrochloride by weight, about 50% to about 940% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

16. An encapsulated, extended release formulation of venlafaxine hydrochloride according to claim 15 having the following dissolution profile in USP Apparatus 1 (basket) at 100 rpm in purified water at 37°C:

Time (hours)	Average % Venlafaxine HCl released
2	<30
4	30-55
8	55-80
12	65-90
24	>80

Office Action Summary	Application No. 08/964,328	Applicant(s) SHERMAN, ET AL.
	Examiner JAMES M. SPEAR	Group Art Unit 1615

☒ Responsive to communication(s) filed on *Nov 5, 1997*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *THREE* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-18* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☒ Claim(s) *11, 13, and 14* is/are allowed.

☒ Claim(s) *1, 15, 17, and 18* is/are rejected.

☒ Claim(s) *2-10, 12, and 16* is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *6*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 15 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 50 to about 70 percent micro-crystalline cellulose, does not reasonably provide enablement for 940 percent microcrystalline cellulose. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This claim appears to be a typographical error, see page 6, line 14.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17 and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 17 and 18 recite the limitation "the spheroids" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claims 17 and 18 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The formulation of claims 17 and 18 improperly depends on claim 14 a method since claim 14 does not recite any limitations describing the formulation.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over McAinsh et al. US 4,138,475 in view of Wong et al. US 5,552,429.

McAinsh et al. shows a hard gelatin capsule comprised spheroids coated with a mixture of ethyl-cellulose and hydroxypropylmethyl-cellulose. The active

agent propranolol is blended with micro-crystalline cellulose. See Abstract, example and claim 1. The reference does not show venlafaxine. Wong et al. is relied on for teaching extended release dosage forms comprised of the same ingredients as McAinsh et al. including the drugs venlafaxine and propranolol. See column 4, lines 7-10, column 6, lines 54-55, column 7, lines 18-22, formulation 5. To use the venlafaxine of Wong et al. in the McAinsh et al. capsule with a reasonable expectation of success would have been obvious to one of ordinary skill in the art. The motivation being a desire to obtain optimum drug efficacy over a prolonged period of time while improving patient compliance by reducing the number of dosages required.

Claims 2-10, 12 and 16 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 11, 13 and 14 are allowed.

Claims 1, 15, 17 and 18 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner James M. Spear whose telephone

number is (703) 308-2457. The examiner can normally be reached on Monday through Friday from 6:30 AM to 12:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K. Page, can be reached on (703) 308-2927. The fax phone number for the organization where this application or proceeding is assigned is (703) 305-3592 or (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

SPEAR; aco

October 5, 1998

James M. Spear
PATENT EXAMINER
ART UNIT 1615

Exhibit 37

US005506270A

United States Patent [19]

Upton et al.

[11] Patent Number: 5,506,270

[45] Date of Patent: Apr. 9, 1996

[54] **VENLAFAXINE IN THE TREATMENT OF HYPOTHALAMIC AMENORRHEA IN NON-DEPRESSED WOMEN**

[75] Inventors: **Gertrude V. Upton**, Radnor; **Albert T. Derivan**, Villanova; **Richard L. Rudolph**, Berwyn, all of Pa.

[73] Assignee: **American Home Products Corporation**, Madison, N.J.

[21] Appl. No.: **380,903**

[22] Filed: **Jan. 30, 1995**

[51] **Int. Cl.**[6] **A61K 31/045**; A01N 31/00

[52] **U.S. Cl.** **514/730**; 564/157; 564/219; 564/336; 549/443; 549/444; 514/646; 514/653; 514/659; 514/727; 514/729; 514/899

[58] **Field of Search** 564/157, 219, 564/336; 549/443, 444; 514/646, 653, 659, 727, 729, 730, 899

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,110,438	8/1978	Gahwyler	424/177
4,291,028	9/1981	Vorys	424/238
4,292,315	9/1981	Vorys	424/240
4,328,134	5/1982	Schally et al.	525/54.11
4,535,186	8/1985	Husbands et al.	564/336
4,611,078	9/1986	Husbands et al.	558/410
4,761,501	8/1988	Husbands et al.	564/167
4,826,844	5/1989	Husbands et al.	514/252

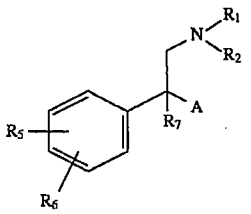
OTHER PUBLICATIONS

Hennert et al., The Lancet, 2, 8614, 789–790, Oct. 1, 1988.
Upton et al., Yale Journal of Biology and Medicine, 46, 314–323, (1973).
Upton, Twelfth Ann. Mtg. of the Int. Soc. of Reproductive Med. Oct. 2–4, 1980.
Berga et al., Journal of Clinical Immunoassay, 14, 1, 23–28, (1991).
Reame et al., Journal of Clinical Endocrinology and Metabolism, 61, 5, 851–858, 1985.
Balen et al., British Journal of Obstetrics and Gynaecology, 100, 1082–1089, Dec. 1993.
Berga et al., Psychiatric Clinics of North America, 12, 1, 105–116, 1989.
Molinksi, Psychother. Psychosom., 31, 283–287, 1979.
Fries et al., Am. J. Obstet. Gynecol., 118, 4, 473–479 (1974).
Schwartz, Journal of Adolescent Health Care, 7, 425 (1986).
Fava et al., Psychosomatics, 25, 12, 905–908, (1984).
Galle et al., Fertility and Sterility, 39, 5, 633–639 (1983).
Cohen et al., Am. J. Psychiatry, 151, 4, 620 (1994).
Leyendecker et al., Human Reproduction, 8, 2, 184–188, (1993).

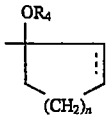
Primary Examiner—Samuel A. Acquah
Attorney, Agent, or Firm—Steven R. Eck

[57] **ABSTRACT**

This invention provides a method for treating hypothalamic amenorrhea in a non-depressed female mammal by administering to the mammal an effective amount of a hydroxycycloalkanephenethyl amine compound of the following structural formula:



in which A is a moiety of the formula



wherein

the dotted line represents optional unsaturation;

R_1 is hydrogen or alkyl;

R_2 is alkyl;

R_4 is hydrogen, alkyl, formyl, or alkanol;

R_5 and R_6 are, independently, hydrogen, hydroxyl, alkyl, alkoxy, alkanoyloxy, cyano, nitro, alkylmercapto, amino, alkylamino, dialkylamino, alkanamido, halo, trifluoromethyl, or taken together, methylene dioxy;

R_7 is hydrogen or alkyl; and

n is 0, 1, 2, 3, or 4;
or a pharmaceutically acceptable salt thereof.

13 Claims, No Drawings

VENLAFAXINE IN THE TREATMENT OF HYPOTHALAMIC AMENORRHEA IN NON-DEPRESSED WOMEN

This invention comprises a new use for venlafaxine. More particularly, this invention comprises a method for treating hypothalamic amenorrhea (HA) in a non-depressed female mammal, preferably in a non-depressed human female.

BACKGROUND OF THE INVENTION

The active ingredients of this invention, (1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol), its analogues or therapeutically acceptable salts thereof, are known generally as venlafaxine. These ingredients are disclosed in U.S. Pat. No. 4,535,186 (Husbands et al.) and have been previously reported to be useful as an antidepressant. U.S. Pat. No. 4,535,186 teaches the production of venlafaxine and its analogues and is incorporated herein by reference.

Venlafaxine has been shown to be a potent inhibitor of monoamine neurotransmitter uptake, a mechanism associated not only with demonstrated clinical antidepressant activity, but also with reproductive function by affecting indirectly the hypothalamic-pituitary-ovarian axis. Due to its novel structure, venlafaxine has a mechanism of action different from other available antidepressants, such as the tricyclic antidepressants desipramine, nortriptyline, protriptyline, imipramine, amitryptyline, trimipramine, and doxepin and different from the serotonin reuptake inhibitors (SRIs), e.g. fluoxetine, sertraline and paroxetine.

It is believed that venlafaxine's mechanism of action is related to potent inhibition of the uptake of the monoamine neurotransmitters serotonin and norepinephrine. To a lesser degree, venlafaxine also inhibits dopamine reuptake, but it has no inhibitory activity on monoamine oxidase. O-desmethylvenlafaxine, venlafaxine's major metabolite in humans, exhibits a similar pharmacologic profile. However, venlafaxine's ability to inhibit norepinephrine and serotonin (5-HT) uptake has been predicted to have an effect not just on depression but also on reproductive function through its neurotransmitter effects on the hypothalamic-pituitary-ovarian (HPO) axis.

DESCRIPTION OF THE INVENTION

The hypophysiotropic area of the hypothalamus is rich in biogenic amines (e.g., norepinephrine (NE), serotonin (5-HT) and dopamine (DA)) that can affect both the central nervous system (CNS) and endocrine system. The synthesis and release of pituitary hormones are controlled by releasing and inhibitory homones that are found in this anatomical area and controlled by the neurotransmitters 5-HT, norepinephrine, and dopamine whose afferents are located in the hypophysiotropic area and originate in the hypothalamus and in higher centers.

Altered levels of central neurotransmitters can result in a dysfunctional CNS and, in some cases, with consequent profound effects on the hypothalamic pituitary axis (HPO) resulting in impaired reproductive function.

An excess of central biogenic amines can result in altered pulse frequency and irregular amplitude of gonadotropin releasing hormone (GnRH) secretion. These changes lead to disruption of GnRH cyclicity and pituitary down-regulation by desensitization of pituitary receptors resulting in impaired secretion of luteinizing hormone (LH) and follicle stimulating hormone (FSH) and consequent impaired gonadal function. On the other hand, a deficiency of central biogenic amines decreases the synthesis and release of GnRH, but cyclicity may be normal. The effects on the pituitary are a decreased number of receptors leading to impaired secretion of LH and FSH and consequent impaired gonadal function. Thus, either excess or deficiency of neurotransmitters (namely, norepinephrine, serotonin and dopamine) may lead to impaired gonadal function.

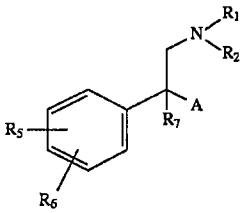
The CNS and Endocrine systems are inextricably linked and psychotropic drugs will invariably have some measurable effect on both systems. However, in the case of hypothalamic amenorrhea, one can determine the direct effect on the hypothalamic hormones by measuring gonadotropin-releasing hormone (GnRH), LH, itself, as well as the more objective endpoint of return of menses. These measures distinguish quite clearly an effective physical endpoint distinct from depression endpoints rendering depression scoring systems irrelevant. This proposed treatment is designed to cure an endocrinopathy with or without accompanying comorbidity (depression). The aim or goal of the therapy is the return of normal reproductive function.

Present therapy for hypothalamic amenorrhea uses GnRH delivered I.V. in pulsatile fashion as well as using other invasive supportive therapy, e.g. injections of human chorionic gonadotropin (HCG). The present invention delivers oral doses without the need for supportive ancillary therapy or the use of invasive techniques.

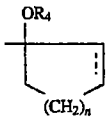
Hypothalamic amenorrhea, also known as secondary amenorrhea is the pathological absence of menstruation due to abnormal centrally mediated neuroendocrine responses affecting the hypothalamic-pituitary-ovarian axis. This cessation of menses may result following a number of occurrences, including severe stress, emotional disturbances or continuous strenuous exercise as in runners or ballet dancers, or sudden loss of body mass (anorexia nervosa), etc. unrelated to depression.

Hypothalamic amenorrhea occurs in about 5% of all menstruating women, with age distribution ranges from approximately 18 years (15%) to 41+ years (21%), reaching a maximum of 52% between ages 22 and 29. It is characterized by low to normal gonadotropins and failure to demonstrate withdrawal bleeding. It is not characterized by depression. Stressful events are known to precipitate amenorrhea and the symptoms can last from a few months to years. Infertility is the usual sequelae following loss of ovulation and menses. This disorder is usually diagnosed by an exclusionary process with particular attention to the existence of pituitary tumors. Patients suffering from hypothalamic amenorrhea have low to normal gonadotropins and some stressful event has often occurred prior to onset of the disorder. The resultant sequelae, i.e., anovulation and amenorrhea, can usually be traced to abnormal Gonadotropin Releasing Hormone (GnRH) rhythms and the restoration of normal rhythm and cyclicity, such as by the practice of the present invention, leads to a resumption of menses, ovulation and hence fertility. The method of the present invention is particularly of interest for the treatment of hypothalamic amenorrhea in non-depressed women who are otherwise physically and mentally normal.

The present invention provides a method for treating hypothalamic amenorrhea in a non-depressed mammal, preferably in a non-depressed human female. This method involves administering to the mammal one or more compounds from a group of substituted phenethylamines following the structural formula:



in which A is a moiety of the formula



wherein

the dotted line represents optional unsaturation;

R_1 is hydrogen or alkyl of 1 to 6 carbon atoms;

R_2 is alkyl of 1 to 6 carbon atoms;

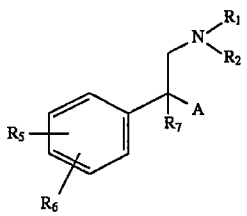
R_4 is hydrogen, alkyl of 1 to 6 carbon atoms, formyl, or alkanol of 2 to 7 carbon atoms;

R_5 and R_6 are independently hydrogen, hydroxyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, cyano, nitro, alkylmercapto of 1 to 6 carbon atoms, amino, alkylamino of 1 to 6 carbon atoms, dialkylamino in which each alkyl group is of 1 to 6 carbon atoms, alkanamido of 2 to 7 carbon atoms, halo, trifluoromethyl, or when taken together, methylene dioxy;

R_7 is hydrogen or alkyl of 1 to 6 carbon atoms; and n is one of the integers 0, 1, 2, 3, or 4;

or a pharmaceutically acceptable salt thereof.

The preferred compounds are those of the formula:



in which

A is as defined supra;

R_1 is hydrogen or alkyl of 1 to 3 carbon atoms;

R_2 is alkyl of 1 to 3 carbon atoms;

R_3 is hydrogen, hydroxy, alkoxy of 1 to 3 carbon atoms, chloro, bromo, trifluoromethyl or alkyl of 1 to 3 carbon atoms;

R_5 is hydrogen, hydroxyl, alkoxy of 1 to 3 carbon atoms, chloro, bromo, trifluoromethyl or alkyl of 1 to 3 carbon atoms;

R_6 is alkyl of 1 to 3 carbon atoms, alkoxy of 1 to 3 carbon atoms, chloro, bromo, trifluoromethyl or alkanoyloxy of 2 to 3 carbon atoms;

R_7 is hydrogen or alkyl of 1 to 3 carbon atoms;

or a pharmaceutically acceptable salt thereof.

The most preferred compounds are those in which both R_5 and R_6 are in meta positions, or one of R_5 and R_6 is in the para position, and n is 2.

Of particular interest are the compounds 1-[(2-dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol and 1-[(2-dimethylamino)-1-(4-hydoxyphenyl)ethyl]cyclohexanol and pharmaceutically acceptable salts thereof.

The compounds in which R_4 is formyl or alkanoyl of 2 to 7 carbon atoms have been found to be not as potent as the corresponding free hydroxy bearing derivatives. However, in long term therapy the acyloxy derivatives will act as pro drugs as the acyl group is removed in vivo either via acid hydrolysis in the stomach or enzymatically.

For the purposes of this disclosure and the claims that follow, it is understood that the use of venlafaxine in treating hypothalamic amenorrhea includes the use of venlafaxine's free base, its pharmaceutically acceptable salts, its racemate and its individual enantiomers, and venlafaxine analogs, both as racemates and as their individual enantiomers.

The pharmaceutically acceptable acid addition salts of the basic compounds of this invention are formed conventionally by reaction of the free base with an equivalent amount of any acid which forms a non-toxic salt. Illustrative acids are either inorganic or organic, including hydrochloric, hydrobromic, fumaric, maleic, succinic, sulfuric, phosphoric, tartaric, acetic, citric, oxalic, and similar acids. For parenteral administration, the use of water soluble salts is preferred, although either the free base of the pharmaceutically acceptable salts are applicable for oral or parenteral administration of the hypothalamic amenorrhea treating agents of this invention. The halo substituent representing R_5 or R_6 is intended to include the chloro, bromo, iodo, or fluoro substituents.

Pharmaceutical compositions containing the compounds of this invention represent an additional aspect of this invention. The active ingredient can be compounded into any of the usual oral dosage forms including tablets, capsules and liquid preparations such as elixirs and suspensions containing various coloring, flavoring, stabilizing and flavor masking substances. For compounding oral dosage forms, the active ingredient can be mixed with various conventional tabletting materials such as starch, calcium carbonate, lactose, sucrose and dicalcium phosphate to aid the tabletting or capsulating process. Magnesium stearate, as an additive, provides a useful lubricant function when desired.

The active ingredients can be dissolved or suspended in a pharmaceutically acceptable sterile liquid carrier, such as sterile water, sterile organic solvent or a mixture of both. Preferably a liquid carrier is one suitable for parenteral injection. Where the active ingredient is sufficiently soluble it can be dissolved in normal saline as a carrier; if it is too insoluble for this it can often be dissolved in a suitable organic solvent, for instance aqueous propylene glycol or polyethylene glycol solutions. Aqueous propylene glycol containing from 10 to 75% of the glycol by weight is generally suitable. In other instances other compositions can be made by dispersing the finely-divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution, or in a suitable oil, for instance arachis oil. Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by intramuscular, intraperitoneal or subcutaneous injection.

Preferably the pharmaceutical composition is in unit dosage form, e.g. as tablets or capsules. In such form, the composition is sub-divided in unit doses containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example, packeted powders or vials or ampoules. The unit dosage form can be a capsule, cachet or tablet itself, or it can be the appropriate number of any of these in package form. The quantity of the active ingredient in a unit dose of composition may be varied or adjusted from about 1 mg. or less to about 25 mg. or more, according to the particular need and the activity of the active ingredient. The usual oral recommended dose of venlafaxine

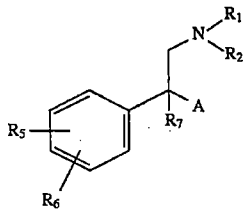
for humans may be between about 25 and about 200 mg/day or higher, not to exceed about 375 mg/day, and this dose may be administered in divided doses, preferably with food if administered orally. A maximum recommended daily dose for humans would be about 225 mg. The treatment regimen may start with the lowest dosage, such as 25 mg, and the dose may be titrated upward incrementally, such as in 25 mg increments, up to the maximum recommended dosage. The incremental increases in dosage may be conducted at monthly intervals until menses is resumed at normal cyclic intervals. At the discretion of the attending physician, the compounds of this invention may also be administered at other than daily doses.

It will be understood by one skilled in the art that doseage under this invention will be determined by the particular circumstances surrounding each case, as will the route of administration (e.g. via an oral route, transdermal route, via a pharmaceutical implant, etc.). It is understood that, while it is preferable that the compounds and pharmaceutical formulations of this invention comprise an oral dosage form, such as capsules or tablets, this invention is intended to cover any means of administration to a patient of an active amount of the compounds listed above in the treatment of hypothalamic amenorrhea. Such administrations may also be provided in a bolus form, intermittent-release form, sustained oral administration form or time-release form, which may be used to spread the doseage over time, such as for once-a-day applications.

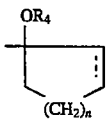
It should also be understood that the present invention is intended to include all methods of, and reasons for, treating hypothalamic amenorrhea in a non-depressed mammal, preferably in a non-depressed human, by administering to the individual an effective amount of venlafaxine or its analogues or pharmaceutically acceptable salts. For the purposes of the present invention, treating hypothalamic amenorrhea is to be understood as covering all prophylactic, therapeutic, progression inhibiting, remedial, maintenance, curative or other administrations, regimens or treatments of or with venlafaxine or its analogues or salts that yield the desired reduction of the effects of hypothalamic amenorrhea in a non-depressed mammal, preferably in a non-depressed human female.

What is claimed:

1. A method of treating hypothalamic amenorrhea in a non-depressed female mammal, the method comprising administering to the non-depressed female mammal an effective amount of a compound of the formula:



in which A is a moiety of the formula



wherein

the dotted line represents optional unsaturation;

R_1 is hydrogen or alkyl of 1 to 6 carbon atoms;

R_2 is alkyl of 1 to 6 carbon atoms;

R_4 is hydrogen, alkyl of 1 to 6 carbon atoms, formyl, or alkanol of 2 to 7 carbon atoms;

R_5 and R_6 are, independently, hydrogen, hydroxyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, cyano, nitro, alkylmercapto of 1 to 6 carbon atoms, amino, alkylamino of 1 to 6 carbon atoms, dialkylamino in which each alkyl group is of 1 to 6 carbon atoms, alkanamido of 2 to 7 carbon atoms, halo, trifluoromethyl, or taken together, methylene dioxy;

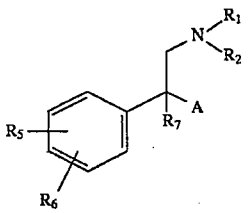
R_7 is hydrogen or alkyl of 1 to 6 carbon atoms; and

n is 0, 1, 2, 3, or 4;

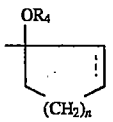
or a pharmaceutically acceptable salt thereof.

2. The method of claim 1 in which the non-depressed female mammal is a human.

3. The method of claim 1 wherein the compound of the formula:



in which A is a moiety of the formula



wherein

the dotted line represents optional unsaturation, and

R_1 is hydrogen or alkyl of 1 to 3 carbon atoms;

R_2 is alkyl of 1 to 3 carbon atoms;

R_5 is hydrogen, hydroxyl, alkoxy of 1 to 3 carbon atoms, chloro, bromo, trifuoromethyl or alkyl of 1 to 3 carbon atoms;

R_6 is alkyl of 1 to 3 carbon atoms, alkoxy of 1 to 3 carbon atoms, chloro, bromo, trifluoromethyl or alkanoyloxy of 2 to 3 carbon atoms;

R_7 is hydrogen or alkyl of 1 to 3 carbon atoms;

or a pharmaceutically acceptable salt thereof.

4. The method of claim 3 wherein R_5 and R_6 are both in meta positions, or one of R_5 and R_6 is in the para position, and n is 2.

5. The method of claim 3 wherein the compound is 1-[(2-dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

6. The method of claim 3 wherein the compound is 1-[2-(dimethylamino)-1-(4-hydroxyphenyl)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

7. The method of claim 3 in which the non-depressed female mammal is a human.

8. The method of claim 1 wherein the effective amount comprises a daily dose of between about 1 mg/day and about 375 mg/day.

9. The method of claim 1 wherein the effective amount comprises a daily dose of between about 25 mg/day and about 225 mg/day.

10. The method of claim 1 wherein the effective amount comprises a daily dose of between about 75 mg/day and about 200 mg/day.

11. The method of claim 3 wherein the effective amount comprises a daily dose of between about 1 mg/day and about 375 mg/day.

12. The method of claim 3 wherein the effective amount comprises a daily dose of between about 25 mg/day and about 225 mg/day.

13. The method of claim 3 wherein the effective amount comprises a daily dose of between about 75 mg/day and about 200 mg/day.

* * * * *

EXHIBIT 38
REDACTED

Exhibit 39

Tables 2 and 3 provide concentration-time data resulting from multiple dose and single dose studies utilizing both the disclosed extended release venlafaxine hydrochloride formulation as well as an immediate release venlafaxine hydrochloride formulation. These data are consistent with the conclusion that the drug in the extended release product is both released and absorbed more slowly than from the immediate release product.

Thus, the patents-in-suit teach formulations that would be reasonably expected to behave *in vivo* in the manner claimed: a formulation having the *in vitro* dissolution profile described in Table 1 would be, according to the patents in suit, reasonably expected to display the *in vivo* characteristics depicted in Tables 2 and 3. Conformance with this profile is expected to provide the requisite *in vivo* therapeutic blood plasma levels over a twenty-four hour period as described in the claims in suit. [*See, e.g.*, col. 6:42-45].

C. The Level of Skill In the Art For the Patents In Suit

Based on my experience in teaching and conducting research in the field of pharmacokinetics for the past 35 years, and my review of the patents in suit, I understand that one of ordinary skill in the art is a person with at least a bachelors degree in pharmacy or some closely related discipline, or a Pharm. D. degree; would have at least two years of work experience in the formulation, design, or evaluation of pharmaceutical dosage forms, including extended release dosage forms; and would have taken courses in biopharmaceutics, pharmacokinetics, and pharmacodynamics or would have acquired comparable knowledge through work experience. Such a person would also have a working

knowledge of, or would know to consult with persons with expertise in (1) the pharmacologic profile, mechanism of action, efficacy and adverse effects of serotonin, norepinephrine, and dopamine reuptake inhibitors in the treatment of psychiatric disorders, (2) the diagnosis and treatment of patients with psychiatric disorders, and (3) biostatistics.

In arriving at this definition, I considered the background and education of colleagues with whom I have interacted in my academic setting as well as in the pharmaceutical industry. I also considered the types of problems faced by scientists who develop and evaluate extended release formulations, design and conduct clinical studies (focusing on bioavailability and bioequivalence), and how these problems were addressed and to what extent they were eventually solved, if at all. I took into account the fact that sometimes such problems were never solved. I also considered the state of the art in the pharmaceutical sciences as it existed in the middle 1990s, particularly as it relates to the design and evaluation of oral dosage forms, the pharmacokinetic analysis of data derived from clinical studies, and the delivery of centrally acting drugs to the brain.

D. The Meaning of Certain Patent Claim Terms

I have considered the meaning of certain claim terms in claims 20 through 25 of the '171 patent, claims 1, 2, 13, and 14 of the '120 patent, and claims 1 through 6 of the '958 patent.

Exhibit 40

HellerEhrman LLP

April 13, 2007

Via E-mail and U.S. Mail

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40443.0005

Linda A. Wadler, Esq.
Finnegan, Henderson, Farabow,
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901 New York Ave., N.W.
Washington, D.C. 20001-4413

Re: *Wyeth v. Impax Laboratories*, No. 06-222 (D. Del.)

Dear Linda:

Pursuant to paragraph 8 of the Court's July 13, 2006 Scheduling Order and the parties' agreements with respect to the same as set forth in Ms. Rudolph's letter of today, the following are Impax's proposed claim constructions:

Claim Term	Impax's Proposed Construction
with diminished incidence(s) of nausea and emesis	a decrease in the number of patients suffering from nausea and vomiting compared to patients receiving the same total daily dose of an immediate release formulation that is administered at least twice a day
extended release formulation	a formulation comprising venlafaxine, microcrystalline cellulose, and, optionally, HPMC coated with a mixture of ethyl cellulose and HPMC in an amount needed to provide a specific unit dosage administered once-a-day to provide a therapeutic blood plasma level of venlafaxine over the entire 24-hour period of administration
for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride	the peak(s) and trough(s) due to the "therapeutic metabolism" of any second or third dose given in a single day is eliminated by dosing only once every 24 hours
spheroid	one or more particles that are generally shaped like a sphere, although they do not have to be perfectly round

Best regards,

Samuel F. Ernst

cc: Jessica R. Wolff, Esq.
Daniel N. Kassabian, Esq.
Eric L. Lane, Esq.
Daralyn J. Durie, Esq.
Asim Bhansali, Esq.
Paula L. Blizzard, Esq.
Mary B. Matterer, Esq.
Basil J. Lewris, Esq.
James K. Hammond, Esq.
Barbara R. Rudolph, Esq.
Karen Jacobs Louden, Esq.

Exhibit 41

Special Accommodations

This meeting is physically accessible to people with disabilities. Requests for sign language interpretation or other auxiliary aids should be directed to Paul J. Howard (see **ADDRESSES**) at least 5 days prior to the meeting date.

Dated: October 3, 2007.

Tracey L. Thompson,

Acting Director, Office of Sustainable Fisheries, National Marine Fisheries Service.

[FR Doc. E7–19823 Filed 10–9–07; 8:45 am]

BILLING CODE 3510–22–S

DEPARTMENT OF COMMERCE

Patent and Trademark Office

[Docket No.: PTO–P–2007–0031]

Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co.* v. *Teleflex Inc.*

AGENCY: United States Patent and Trademark Office, Commerce.

ACTION: Notice.

SUMMARY: The United States Patent and Trademark Office (USPTO) is publishing examination guidelines for determining obviousness under 35 U.S.C. 103 in view of the Supreme Court decision in *KSR International Co.* v. *Teleflex Inc.* These guidelines will assist USPTO personnel to make a proper determination of obviousness under 35 U.S.C. 103 and to provide an appropriate supporting rationale.

DATES: These guidelines are effective October 10, 2007.

FOR FURTHER INFORMATION CONTACT: Contact either Kathleen Kahler Fonda, Legal Advisor (telephone (571) 272–7754; e-mail *kathleen.fonda@uspto.gov*) or Pinchus M. Laufer, Patent Examination Policy Analyst (telephone (571) 272–7726; e-mail *pinchus.laufer@uspto.gov*), of the Office of the Deputy Commissioner for Patent Examination Policy. Alternatively, mail may be addressed to Ms. Fonda or Mr. Laufer at Commissioner for Patents, attn: KSR, P.O. Box 1450, Alexandria, VA 22313–1450.

SUPPLEMENTARY INFORMATION: These guidelines are intended to assist Office personnel to make a proper determination of obviousness under 35 U.S.C. 103, and to provide an appropriate supporting rationale in view of the recent decision by the Supreme Court in *KSR International Co.* v. *Teleflex Inc.* (KSR).[1] The guidelines are based on the Office's current understanding of the law, and are believed to be fully consistent with the binding precedent of the Supreme Court.[2]

These guidelines do not constitute substantive rule making and hence do not have the force and effect of law. They have been developed as a matter of internal Office management and are not intended to create any right or benefit, substantive or procedural, enforceable by any party against the Office. Rejections will continue to be based upon the substantive law, and it is these rejections that are appealable. Consequently, any failure by Office personnel to follow the guidelines is neither appealable nor petitionable.

To the extent that earlier guidance from the Office, including certain sections of the current Manual of Patent Examining Procedure (MPEP), is inconsistent with the guidance set forth herein, Office personnel are to follow these guidelines. The next revision of the MPEP will be updated accordingly.

I. The *KSR* Decision and Principles of the Law of Obviousness

Teleflex owned a patent claiming technology useful in the gas pedal of a car. The invention at issue in *KSR* was a pedal assembly that could be adjusted to accommodate drivers of different statures. The electronic pedal-position sensor was positioned on the support for the pedal assembly, and the pivot point of the pedal remained fixed regardless of how the pedal assembly was adjusted. This combination of the fixed pivot point for the adjustable pedal and the fixed sensor position on the support resulted in a simpler, lighter, and more compact design.

Teleflex sued KSR for infringement. The district court cited references that separately taught adjustable pedals and sensors, and found on summary judgment that Teleflex's patent was invalid for obviousness. On appeal, the Federal Circuit vacated the district court's decision, and remanded the case. The Federal Circuit stated that "the district court's analysis applied an incomplete teaching-suggestion-motivation test" in arriving at the finding of obviousness.[3]

Upon KSR's petition for review of the Federal Circuit's decision, the Supreme Court reversed, concluding that the district court had correctly determined that the patent was invalid for obviousness. The Supreme Court reaffirmed the familiar framework for determining obviousness as set forth in *Graham* v. *John Deere Co.*, but stated that the Federal Circuit had erred by applying the teaching-suggestion-motivation (TSM) test in an overly rigid and formalistic way.[4] Specifically, the Supreme Court stated that the Federal Circuit had erred in four ways: (1) "By holding that courts and patent examiners should look only to the problem the patentee was trying to solve;" [5] (2) by assuming "that a person of ordinary skill attempting to solve a problem will be led only to those elements of prior art designed to solve the same problem;" [6] (3) by concluding "that a patent claim cannot be proved obvious merely by showing that the combination of elements was 'obvious to try;' " [7] and (4) by overemphasizing "the risk of courts and patent examiners falling prey to hindsight bias" and as a result applying "[r]igid preventative rules that deny factfinders recourse to common sense." [8]

In *KSR*, the Supreme Court particularly emphasized "the need for caution in granting a patent based on the combination of elements found in the prior art," [9] and discussed circumstances in which a patent might be determined to be obvious. Importantly, the Supreme Court reaffirmed principles based on its precedent that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." [10] The Supreme Court stated that there are "[t]hree cases decided after *Graham* [that] illustrate this doctrine." [11] (1) "In *United States* v. *Adams*, * * * [t]he Court recognized that when a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result." [12] (2) "In *Anderson's-Black Rock, Inc.* v. *Pavement Salvage Co.*, * * * [t]he two [pre-existing elements] in combination did no more than they would in separate, sequential operation." [13] (3) "[I]n *Sakraida* v. *AG Pro, Inc.*, the Court derived * * * the conclusion that when

[1] 550 U.S. _, 82 USPQ2d 1385 (2007).

[2] Further developments in the law of obviousness are to be expected in view of *KSR*. Thus, it is not clear which Federal Circuit decisions will retain their viability.

[3] *Teleflex Inc.* v. *KSR Int'l Co.*, 119 Fed. Appx. 282, 288 (Fed. Cir. 2005).

[4] *KSR*, 550 U.S. at __, 82 USPQ2d at 1391.

[5] *Id.* at __, 82 USPQ2d at 1397.

[6] *Id.*

[7] *Id.*

[8] *Id.*

[9] *Id.* at __, 82 USPQ2d at 1395.

[10] *Id.*

[11] *Id.*

[12] *Id.*

[13] *Id.*

a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious." [14] (Internal quotations omitted.) The principles underlying these cases are instructive when the question is whether a patent application claiming the combination of elements of prior art would have been obvious. The Supreme Court further stated that:

When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, 35 U.S.C. 103 bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.[15]

When considering obviousness of a combination of known elements, the operative question is thus "whether the improvement is more than the predictable use of prior art elements according to their established functions." [16]

II. The Basic Factual Inquiries of *Graham* v. *John Deere Co*

An invention that would have been obvious to a person of ordinary skill at the time of the invention is not patentable.[17] As reiterated by the Supreme Court in *KSR*, the framework for the objective analysis for determining obviousness under 35 U.S.C. 103 is stated in *Graham* v. *John Deere Co.*[18] Obviousness is a question of law based on underlying factual inquiries. The factual inquiries enunciated by the Court are as follows:

(1) Determining the scope and content of the prior art;

(2) Ascertaining the differences between the claimed invention and the prior art; and

(3) Resolving the level of ordinary skill in the pertinent art.

Objective evidence relevant to the issue of obviousness must be evaluated by Office personnel.[19] Such evidence, sometimes referred to as "secondary considerations," may include evidence of commercial success, long-felt but unsolved needs, failure of others, and unexpected results. The evidence may be included in the specification as filed, accompany the application on filing, or be provided in a timely manner at some other point during the prosecution. The weight to be given any objective evidence is decided on a case-by-case basis. The mere fact that an applicant has presented evidence does not mean that the evidence is dispositive of the issue of obviousness.

The question of obviousness must be resolved on the basis of these factual determinations. While each case is different and must be decided on its own facts, the *Graham* factors, including secondary considerations when present, are the controlling inquiries in any obviousness analysis.[20] As stated by the Supreme Court in *KSR*, "While the sequence of these questions might be reordered in any particular case, the [*Graham*] factors continue to define the inquiry that controls." [21]

Office Personnel as Factfinders

Office personnel fulfill the critical role of factfinder when resolving the *Graham* inquiries. It must be remembered that while the ultimate determination of obviousness is a legal conclusion, the underlying *Graham* inquiries are factual. When making an obviousness rejection, Office personnel must therefore ensure that the written record includes findings of fact concerning the state of the art and the teachings of the references applied. In certain circumstances, it may also be important to include explicit findings as to how a person of ordinary skill would have understood prior art teachings, or what a person of ordinary skill would have known or could have done. Factual findings made by Office personnel are the necessary underpinnings to establish obviousness.

Once the findings of fact are articulated, Office personnel must provide an explanation to support an obviousness rejection under 35 U.S.C. 103. 35 U.S.C. 132 requires that the applicant be notified of the reasons for the rejection of the claim so that he or she can decide how best to proceed. Clearly setting forth findings of fact and the rationale(s) to support a rejection in an Office action leads to the prompt resolution of issues pertinent to patentability.[22]

In short, the focus when making a determination of obviousness should be on what a person of ordinary skill in the pertinent art would have known at the time of the invention, and on what such a person would have reasonably expected to have been able to do in view of that knowledge. This is so regardless of whether the source of that knowledge and ability was documentary prior art, general knowledge in the art, or common sense. What follows is a discussion of the *Graham* factual inquiries.

A. Determining the Scope and Content of the Prior Art

In determining the scope and content of the prior art, Office personnel must first obtain a thorough understanding of the invention disclosed and claimed in the application under examination by reading the specification, including the claims, to understand what the applicant has invented.[23] The scope of the claimed invention must be clearly determined by giving the claims the "broadest reasonable interpretation consistent with the specification." [24] Once the scope of the claimed invention is determined, Office personnel must then determine what to search for and where to search.

1. *What to search for:* The search should cover the claimed subject matter and should also cover the disclosed features which might reasonably be expected to be claimed.[25] Although a rejection need not be based on a teaching or suggestion to combine, a preferred search will be directed to finding references that provide such a teaching or suggestion if they exist.

2. *Where to search:* Office personnel should continue to follow the general search guidelines set forth in MPEP § 904 to § 904.03 regarding search of the prior art. Office personnel are reminded that, for purposes of 35 U.S.C. 103, prior art can be either in the field of applicant's endeavor or be reasonably pertinent to the particular problem with which the applicant was concerned. Furthermore, prior art that is in a field of endeavor other than that of the applicant,[26] or solves a problem which

[14] *Id.* at __, 82 USPQ2d at 1395–96.

[15] *Id.* at __, 82 USPQ2d at 1396.

[16] *Id.*

[17] 35 U.S.C. 103(a).

[18] 383 U.S. 1, 148 USPQ 459 (1966).

[19] *Id.* at 17–18, 148 USPQ at 467.

[20] The *Graham* factors were reaffirmed and relied upon by the Supreme Court in its consideration and determination of obviousness in the fact situation presented in *KSR*, 550 U.S. at __, 82 USPQ2d at 1391. The Supreme Court has utilized the *Graham* factors in each of its obviousness decisions since *Graham*. *See Sakraida* v. *Ag Pro, Inc.*, 425 U.S. 273, 189 USPQ 449, reh'g denied, 426 U.S. 955 (1976); *Dann* v. *Johnston*, 425 U.S. 219, 189 USPQ 257 (1976); and *Anderson's-Black Rock, Inc.* v. *Pavement Salvage Co.*, 396 U.S. 57, 163 USPQ 673 (1969).

[21] *KSR*, 550 U.S. at __, 82 USPQ2d at 1391.

[22] These guidelines focus on the proper content of an obviousness rejection, and should not be construed as dictating any particular format.

[23] *See* MPEP § 904 (8th edition, revision 5, August 2006).

[24] *See Phillips* v. *AWH Corp.*, 415 F.3d 1303, 1316, 75 USPQ2d 1321, 1329 (Fed. Cir. 2005) and MPEP § 2111.

[25] *See* MPEP § 904.02.

[26] As noted by the Court in *KSR*, "[w]hen a work is available in one field of endeavor, design

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is different from that which the applicant was trying to solve, may also be considered for the purposes of 35 U.S.C. 103.[27]

For a discussion of what constitutes prior art, see MPEP § 901 to § 901.06(d) and § 2121 to § 2129.

B. Ascertaining the Differences Between the Claimed Invention and the Prior Art

Ascertaining the differences between the claimed invention and the prior art requires interpreting the claim language,[28] and considering both the invention and the prior art as a whole.[29]

C. Resolving the Level of Ordinary Skill in the Art

Any obviousness rejection should include, either explicitly or implicitly in view of the prior art applied, an indication of the level of ordinary skill. A finding as to the level of ordinary skill may be used as a partial basis for a resolution of the issue of obviousness.

The person of ordinary skill in the art is a hypothetical person who is presumed to have known the relevant art at the time of the invention. Factors that may be considered in determining the level of ordinary skill in the art may include: (1) "Type of problems encountered in the art;" (2) "prior art solutions to those problems;" (3) "rapidity with which innovations are made;" (4) "sophistication of the technology;" and (5) "educational level of active workers in the field. In a given case, every factor may not be present, and one or more factors may predominate." [30]

"A person of ordinary skill in the art is also a person of ordinary creativity, not an automaton." [31] "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." [32] Office personnel may also take into account "the inferences and creative steps that a person of ordinary skill in the art would employ." [33]

In addition to the factors above, Office personnel may rely on their own technical expertise to describe the knowledge and skills of a person of ordinary skill in the art.[34]

III. Rationales To Support Rejections Under 35 U.S.C. 103

Once the *Graham* factual inquiries are resolved, Office personnel must determine whether the claimed invention would have been obvious to one of ordinary skill in the art.

> The obviousness analysis cannot be confined by * * * overemphasis on the importance of published articles and the explicit content of issued patents * * *. In many fields it may be that there is little discussion of obvious techniques or combinations, and it often may be the case that market demand, rather than scientific literature, will drive design trends.[35]

Prior art is not limited just to the references being applied, but includes the understanding of one of ordinary skill in the art. The prior art reference (or references when combined) need not teach or suggest all the claim limitations; however, Office personnel must explain why the difference(s) between the prior art and the claimed invention would have been obvious to one of ordinary skill in the art. The "mere existence of differences between the prior art and an invention does not establish the invention's nonobviousness." [36] The gap between the prior art and the claimed invention may not be "so great as to render the [claim] nonobvious to one reasonably skilled in the art." [37] In determining obviousness, neither the particular motivation to make the claimed invention nor the problem the inventor is solving controls. The proper analysis is whether the claimed invention would have been obvious to one of ordinary skill in the art after consideration of all the facts.[38] Factors other than the disclosures of the cited prior art may provide a basis for concluding that it would have been obvious to one of ordinary skill in the art to bridge the gap. The rationales discussed below outline reasoning that may be applied to find obviousness in such cases.

If the search of the prior art and the resolution of the *Graham* factual inquiries reveal that an obviousness rejection may be made using the familiar teaching-suggestion-motivation (TSM) rationale, then such a rejection using the TSM rationale can still be made. Although the Supreme Court in *KSR* cautioned against an overly rigid application of TSM, it also recognized that TSM was one of a number of valid rationales that could be used to determine obviousness.[39] Office personnel should also consider whether one or more of the other rationales set forth below support a conclusion of obviousness.[40] Note that the list of rationales provided below is not intended to be an all-inclusive list. Other rationales to support a conclusion of obviousness may be relied upon by Office personnel.

The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR* noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Court quoting *In re Kahn* [41] stated that " '[R]ejections on obviousness cannot be sustained by

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incentives and other market forces can prompt variations of it, either in the same field or a *different one*." (Emphasis added) 550 U.S. at_, 82 USPQ2d at 1396.

[27] The Court in *KSR* stated that "[t]he first error * * * in this case was * * * holding that courts and patent examiners should look only to the problem the patentee was trying to solve. The Court of Appeals failed to recognize that the problem motivating the patentee may be only one of many addressed by the patent's subject matter * * *. The second error [was] * * * that a person of ordinary skill attempting to solve a problem will be led only to those elements of prior art designed to solve the same problem." 550 U.S. at __, 82 USPQ2d at 1397. Federal Circuit case law prior to the Supreme Court's decision in *KSR* is generally in accord with these statements by the *KSR* Court. *See, e.g., In re Dillon*, 919 F.2d 688, 693, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990) (en banc) ("[I]t is not necessary in order to establish a *prima facie* case of obviousness that both a structural similarity between a claimed and prior art compound (or a key component of a composition) be shown and that there be a suggestion in or expectation from the prior art that the claimed compound or composition will have the same or a similar utility as one newly discovered by applicant."); *In re Lintner*, 458 F.2d 1013, 1018, 173 USPQ 560, 562 (CCPA 1972) ("The fact that [applicant] uses sugar for a different purpose does not alter the conclusion that its use in a prior art composition would be *prima facie* obvious from the purpose disclosed in the references.").

[28] *See* MPEP § 2111.

[29] *See* MPEP § 2141.02.

[30] *In re GPAC*, 57 F.3d 1573, 1579, 35 USPQ2d 1116, 1121 (Fed. Cir. 1995); *Custom Accessories, Inc.* v. *Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 962, 1 USPQ2d 1196, 1201 (Fed. Cir. 1986); *Envtl. Designs, Ltd.* v. *Union Oil Co.*, 713 F.2d 693, 696, 218 USPQ 865, 868 (Fed. Cir. 1983).

[31] *KSR*, 550 U.S. at __, 82 USPQ2d at 1397.

[32] *Id.*

[33] *Id.* at __, 82 USPQ2d at 1396.

[34] The Federal Circuit has stated that examiners and administrative patent judges on the Board are "persons of scientific competence in the fields in which they work" and that their findings are "informed by their scientific knowledge, as to the meaning of prior art references to persons of ordinary skill in the art." *In re Berg*, 320 F.3d 1310, 1315, 65 USPQ2d 2003, 2007 (Fed. Cir. 2003).

[35] *KSR*, 550 U.S. at__, 82 USPQ2d at 1396.

[36] *Dann* v. *Johnston*, 425 U.S. 219, 230, 189 USPQ 257, 261 (1976).

[37] *Id.*

[38] 35 U.S.C. 103(a).

[39] According to the Supreme Court, establishment of the TSM approach to the question of obviousness "captured a helpful insight." 550 U.S. at __, 82 USPQ2d 1385, 1396 (citing *In re Bergel*, 292 F.2d 955, 956–57, 130 USPQ 206, 207–08 (1961)). Furthermore, the Court explained that "[t]here is no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis." *KSR*, 550 U.S. at __, 82 USPQ2d at 1396. The Supreme Court also commented that the Federal Circuit "no doubt has applied the test in accord with these principles [set forth in *KSR*] in many cases." *Id.* at __, 82 USPQ2d at 1396.

[40] The Court in *KSR* identified a number of rationales to support a conclusion of obviousness which are consistent with the proper "functional approach" to the determination of obviousness as laid down in Graham. *Id.* at __, 82 USPQ2d at 1395–97.

[41] 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006).

mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'" [42]

Rationales

(A) Combining prior art elements according to known methods to yield predictable results;

(B) Simple substitution of one known element for another to obtain predictable results;

(C) Use of known technique to improve similar devices (methods, or products) in the same way;

(D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;

(E) "Obvious to try"—choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;

(F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations would have been predictable to one of ordinary skill in the art;

(G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

The subsections below include discussions of each rationale along with examples illustrating how the cited rationales may be used to support a finding of obviousness. The cases cited (from which the facts were derived) may not necessarily stand for the proposition that the particular rationale is the basis for the court's holding of obviousness. Note that, in some instances, a single case is used in different subsections to illustrate the use of more than one rationale to support a finding of obviousness. It may often be the case that, once the *Graham* inquiries have been satisfactorily resolved, a conclusion of obviousness may be supported by more than one line of reasoning.

A. Combining Prior Art Elements According to Known Methods To Yield Predictable Results

To reject a claim based on this rationale, Office personnel must resolve the *Graham* factual inquiries. Office personnel must then articulate the following:

(1) a finding that the prior art included each element claimed, although not necessarily in a single prior art reference, with the only difference between the claimed invention and the prior art being the lack of actual combination of the elements in a single prior art reference;

(2) a finding that one of ordinary skill in the art could have combined the elements as claimed by known methods, and that in combination, each element merely would have performed the same function as it did separately;

(3) a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable; and

(4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

The rationale to support a conclusion that the claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art at the time of the invention.[43] "[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." [44] If any of these findings cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art.

Example 1: The claimed invention in *Anderson's-Black Rock, Inc.* v. *Pavement Salvage Co.*[45] was a paving machine which combined several well-known elements onto a single chassis. Standard prior art paving machines typically combined equipment for spreading and shaping asphalt onto a single chassis. The patent claim included the well-known element of a radiant-heat burner attached to the side of the paver for the purpose of preventing cold joints during continuous strip paving.[46] All of the component parts were known in the prior art. The only difference was the combination of the "old elements" into a single device by mounting them on a single chassis. The Court found that the operation of the heater was in no way dependent on the operation of the other equipment, and that a separate heater could also be used in conjunction with a standard paving machine to achieve the same results. The Court concluded that "[t]he convenience of putting the burner together with the other elements in one machine, though perhaps a matter of great convenience, did not produce a 'new' or 'different function'" [47] and that to those skilled in the art the use of the old elements in combination would have been obvious.

Note that combining known prior art elements is not sufficient to render the claimed invention obvious if the results would not have been predictable to one of ordinary skill in the art.[48] "When the prior art teaches away from combining certain known elements, discovery of successful means of combining them is more likely to be nonobvious." [49]

Example 2: The claimed invention in *Ruiz* v. *AB Chance Co.*[50] was directed to a system which employs a screw anchor for underpinning existing foundations and a metal bracket to transfer the building load onto the screw anchor. The prior art (Fuller) used screw anchors for underpinning existing structural foundations. Fuller used a concrete haunch to transfer the load of the foundation to the screw anchor. The prior art (Gregory) used a push pier for underpinning existing structural foundations. Gregory taught a method of transferring load using a bracket, specifically, a metal bracket transfers the foundation load to the push pier. The pier is driven into the ground to support the load. Neither reference showed the two elements of the claimed invention—screw anchor and metal bracket—used together. The court found that "artisans knew that a foundation underpinning system requires a means of connecting the foundation to the load-bearing member." [51]

The nature of the problem to be solved—underpinning unstable foundations—as well as the need to connect the member to the foundation to accomplish this goal, would have led one of ordinary skill in the art to choose an appropriate load bearing member and a compatible attachment. Therefore, it would have been obvious to use a metal bracket (as shown in Gregory) in combination with the screw anchor (as

[42] *KSR*, 550 U.S. at __, 82 USPQ2d at 1396.

[43] *Id.* at __, 82 USPQ2d at 1395; *Sakraida* v. *AG Pro, Inc.*, 425 U.S. 273, 282, 189 USPQ 449, 453 (1976); *Anderson's-Black Rock, Inc.* v. *Pavement Salvage Co.*, 396 U.S. 57, 62–63, 163 USPQ 673, 675 (1969); *Great Atl. & Pac. Tea Co.* v. *Supermarket Equip. Corp.*, 340 U.S. 147, 152, 87 USPQ 303, 306 (1950).

[44] *KSR*, 550 U.S. at __, 82 USPQ2d at 1396.

[45] 396 U.S. 57, 163 USPQ 673 (1969).

[46] The prior art used radiant heat for softening the asphalt to make patches, but did not use radiant heat burners to achieve continuous strip paving.

[47] *Id.* at 60, 163 USPQ at 674.

[48] *United States* v. *Adams*, 383 U.S. 39, 51–52, 148 USPQ 479, 483 (1966). In *Adams*, the claimed invention was to a battery with one magnesium electrode and one cuprous chloride electrode that could be stored dry and activated by the addition of plain water or salt water. Although magnesium and cuprous chloride were individually known battery components, the Court concluded that the claimed battery was nonobvious. The Court stated that "[d]espite the fact that each of the elements of the Adams battery was well known in the prior art, to combine them as did Adams required that a person reasonably skilled in the prior art must ignore" the teaching away of the prior art that such batteries were impractical and that water-activated batteries were successful only when combined with electrolytes detrimental to the use of magnesium electrodes. *Id.* at 42–43, 50–52, 148 USPQ at 480, 483.

[49] *KSR*, 550 U.S. at __, 82 USPQ2d at 1395.

[50] 357 F.3d 1270, 69 USPQ2d 1686 (Fed. Cir. 2004).

[51] *Id.* at 1276, 69 USPQ2d at 1691.

shown in Fuller) to underpin unstable foundations.

B. Simple Substitution of One Known Element for Another To Obtain Predictable Results

To reject a claim based on this rationale, Office personnel must resolve the *Graham* factual inquiries. Office personnel must then articulate the following:

(1) a finding that the prior art contained a device (method, product, etc.) which differed from the claimed device by the substitution of some components (step, element, etc.) with other components;

(2) a finding that the substituted components and their functions were known in the art;

(3) a finding that one of ordinary skill in the art could have substituted one known element for another, and the results of the substitution would have been predictable; and

(4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

The rationale to support a conclusion that the claim would have been obvious is that the substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. If any of these findings cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art.

Example 1: The claimed invention in *In re Fout*[52] was directed to a method for decaffeinating coffee or tea. The prior art (Pagliaro) method produced a decaffeinated vegetable material and trapped the caffeine in a fatty material (such as oil). The caffeine was then removed from the fatty material by an aqueous extraction process. Applicant (Fout) substituted an evaporative distillation step for the aqueous extraction step. The prior art (Waterman) suspended coffee in oil and then directly distilled the caffeine through the oil. The court found that "[b]ecause both Pagliaro and Waterman teach a method for separating caffeine from oil, it would have been *prima facie* obvious to substitute one method for the other. Express suggestion to substitute one equivalent for another need not be present to render such substitution obvious."[53]

Example 2: The invention in *In re O'Farrell*[54] was directed to a method for synthesizing a protein in a transformed bacterial host species by substituting a heterologous gene for a gene native to the host species. Generally speaking, protein synthesis *in vivo* follows the path of DNA to RNA to protein. Although the prior art Polisky article (authored by two of the three inventors of the application) had explicitly suggested employing the method described for protein synthesis, the inserted heterologous gene exemplified in the article was one that normally did not proceed all the way to the protein production step, but instead terminated with the RNA. A second reference to Bahl had described a general method of inserting chemically synthesized DNA into a plasmid. Thus, it would have been obvious to one of ordinary skill in the art to replace the prior art gene with another gene known to lead to protein production, because one of ordinary skill in the art would have been able to carry out such a substitution, and the results were reasonably predictable.

In response to applicant's argument that there had been significant unpredictability in the field of molecular biology at the time of the invention, the court stated that the level of skill was quite high and that the teachings of Polisky, even taken alone, contained detailed enabling methodology and included the suggestion that the modification would be successful for synthesis of proteins.

This is not a situation where the rejection is a statement that it would have been "obvious to try" without more. Here there was a reasonable expectation of success. "Obviousness does not require absolute predictability of success."[55]

Example 3: The fact pattern in *Ruiz* v. *AB Chance Co.*[56] is set forth above in Example 2 in subsection III.A.

The prior art showed differing load-bearing members and differing means of attaching the foundation to the member. Therefore, it would have been obvious to one of ordinary skill in the art to substitute the metal bracket taught in Gregory for Fuller's concrete haunch for the predictable result of transferring the load.

Example 4: The claimed invention in *Ex parte Smith*[57] was a pocket insert for a bound book made by gluing a base sheet and a pocket sheet of paper together to form a continuous two-ply seam defining a closed pocket. The prior art (Wyant) disclosed at least one pocket formed by folding a single sheet and securing the folder portions along the inside margins using any convenient bonding method. The prior art (Wyant) did not disclose bonding the sheets to form a continuous two-ply seam. The prior art (Dick) disclosed a pocket that is made by stitching or otherwise securing two sheets along three of its four edges to define a closed pocket with an opening along its fourth edge.

In considering the teachings of Wyant and Dick, the Board "found that (1) each of the claimed elements is found within the scope and content of the prior art; (2) one of ordinary skill in the art could have combined the elements as claimed by methods known at the time the invention was made; and (3) one of ordinary skill in the art would have recognized at the time the invention was made that the capabilities or functions of the combination were predictable." Citing *KSR*, the Board concluded that "[t]he substitution of the continuous, two-ply seam of Dick for the folded seam of Wyant thus is no more than 'the simple substitution of one known element for another or the mere application of a known technique to a piece of prior art ready for improvement.'"

C. Use of Known Technique To Improve Similar Devices (Methods, or Products) in the Same Way

To reject a claim based on this rationale, Office personnel must resolve the *Graham* factual inquiries. Office personnel must then articulate the following:

(1) a finding that the prior art contained a "base" device (method, or product) upon which the claimed invention can be seen as an "improvement;"

(2) a finding that the prior art contained a "comparable" device (method, or product that is not the same as the base device) that was improved in the same way as the claimed invention;

(3) a finding that one of ordinary skill in the art could have applied the known "improvement" technique in the same way to the "base" device (method, or product) and the results would have been predictable to one of ordinary skill in the art; and

(4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

The rationale to support a conclusion that the claim would have been obvious is that a method of enhancing a particular class of devices (methods, or products) was made part of the ordinary capabilities of one skilled in the art based upon the teaching of such improvement in other situations. One of ordinary skill in the art would have been capable of applying this known method of enhancement to a "base" device (method, or product) in the prior art and the results would have been predictable to one of ordinary skill in the art. The Supreme Court in *KSR* noted that if the actual application of the technique would have been beyond the skill of one of ordinary skill in the art, then using the technique would not have been obvious.[58] If any of these findings cannot be made, then this

[52] 675 F.2d 297, 213 USPQ 532 (CCPA 1982).

[53] *Id.* at 301, 213 USPQ at 536.

[54] 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988).

[55] *Id.* at 903, 7 USPQ2d at 1681.

[56] 357 F.3d 1270, 69 USPQ2d 1686 (Fed. Cir. 2004).

[57] 83 USPQ2d 1509 (Bd. Pat. App. & Int. 2007).

[58] *KSR*, 550 U.S. at __, 82 USPQ2d at 1396.

rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art.

Example 1: The claimed invention in *In re Nilssen* [59] was directed to a "means by which the self-oscillating inverter in a power-line-operated inverter-type fluorescent lamp ballast is disabled in case the output current from the inverter exceeds some pre-established threshold level for more than a very brief period." [60] That is, the current output was monitored, and if the current output exceeded some threshold for a specified short time, an actuation signal was sent and the inverter was disabled to protect it from damage.

The prior art (a USSR certificate) described a device for protecting an inverter circuit in an undisclosed manner via a control means. The device indicated the high-load condition by way of the control means, but did not indicate the specific manner of overload protection. The prior art (Kammiller) disclosed disabling the inverter in the event of a high-load current condition in order to protect the inverter circuit. That is, the overload protection was achieved by disabling the inverter by means of a cutoff switch.

The court found "it would have been obvious to one of ordinary skill in the art to use the threshold signal produced in the USSR device to actuate a cutoff switch to render the inverter inoperative as taught by Kammiller." [61] That is, using the known technique of a cutoff switch for protecting a circuit to provide the protection desired in the inverter circuit of the USSR document would have been obvious to one of ordinary skill.

Example 2: The fact pattern in *Ruiz* v. *AB Chance Co.*[62] is set forth above in Example 2 in subsection III.A.

The nature of the problem to be solved may lead inventors to look at references relating to possible solutions to that problem.[63] Therefore, it would have been obvious to use a metal bracket (as shown in Gregory) with the screw anchor (as shown in Fuller) to underpin unstable foundations.

D. Applying a Known Technique to a Known Device (Method, or Product) Ready for Improvement To Yield Predictable Results

To reject a claim based on this rationale, Office personnel must resolve the *Graham* factual inquiries. Office personnel must then articulate the following:

(1) a finding that the prior art contained a "base" device (method, or product) upon which the claimed invention can be seen as an "improvement;"

(2) a finding that the prior art contained a known technique that is applicable to the base device (method, or product);

(3) a finding that one of ordinary skill in the art would have recognized that applying the known technique would have yielded predictable results and resulted in an improved system; and

(4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

The rationale to support a conclusion that the claim would have been obvious is that a particular known technique was recognized as part of the ordinary capabilities of one skilled in the art. One of ordinary skill in the art would have been capable of applying this known technique to a known device (method, or product) that was ready for improvement and the results would have been predictable to one of ordinary skill in the art. If any of these findings cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art.

Example 1: The claimed invention in *Dann* v. *Johnston* [64] was directed towards a system (*i.e.*, computer) for automatic record keeping of bank checks and deposits. In this system, a customer would put a numerical category code on each check or deposit slip. The check processing system would record these on the check in magnetic ink, just as it did for amount and account information. With this system in place, the bank can provide statements to customers that are broken down to give subtotals for each category. The claimed system also allowed the bank to print reports according to a style requested by the customer. As characterized by the Court, "[u]nder respondent's invention, then, a general purpose computer is programmed to provide bank customers with an individualized and categorized breakdown of their transactions during the period in question." [65]

Base System—The nature of the current use of data processing equipment and computer software in the banking industry was that banks routinely did much of the record keeping automatically. In routine check processing, the system read any magnetic ink characters identifying the account and routing. The system also read the amount of the check and then printed that value in a designated area of the check. The check was then sent through a further data processing step which used the magnetic ink information to generate the appropriate records for transactions and for posting to the appropriate accounts. These systems included generating periodic statements for each account, such as the monthly statement sent to checking account customers.

Improved System—The claimed invention supplemented this system by recording a category code which can then be utilized to track expenditures by category. Again, the category code will be a number recorded on the check (or deposit slip) which will be read, converted into a magnetic ink imprint, and then processed in the data system to include the category code. This enabled reporting of data by category as opposed to only allowing reporting by account number.

Known Technique—This is an application of a technique from the prior art—the use of account numbers (generally used to track an individual's total transactions) to solve the problem of how to track categories of expenditures to more finely account for a budget. That is, account numbers (identifying data capable of processing in the automatic data processing system) were used to distinguish between different customers. Furthermore, banks have long segregated debits attributable to service charges within any given separate account and have rendered their customers subtotals for those charges. Previously, one would have needed to set up separate accounts for each category and thus receive separate reports. Supplementing the account information with additional digits (the category codes) solved the problem by effectively creating a single account that can be treated as distinct accounts for tracking and reporting services. That is, the category code merely allowed what might previously have been separate accounts to be handled as a single account, but with a number of sub-accounts indicated in the report.

The basic technique of putting indicia on data which then enabled standard sorting, searching, and reporting would have yielded no more than the predictable outcome which one of ordinary skill would have expected to achieve with this common tool of the trade and was therefore an obvious expedient. The Court held that "[t]he gap between the prior art and respondent's system is simply not so great as to render the system nonobvious to one reasonably skilled in the art." [66]

[59] 851 F.2d 1401, 7 USPQ2d 1500 (Fed. Cir. 1988).

[60] *Id.* at 1402, 7 USPQ2d at 1501.

[61] *Id.* at 1403, 7 USPQ2d at 1502.

[62] 357 F.3d 1270, 69 USPQ2d 1686 (Fed. Cir. 2004).

[63] *Id.* at 1277, 69 USPQ2d at 1691.

[64] 425 U.S. 219, 189 USPQ 257 (1976).

[65] *Id.* at 222, 189 USPQ at 259.

[66] *Id.* at 230, 189 USPQ at 261.

Example 2: The fact pattern in *In re Nilssen*[67] is set forth above in Example 1 in subsection III.C.

The court found "it would have been obvious to one of ordinary skill in the art to use the threshold signal produced in the USSR device to actuate a cutoff switch to render the inverter inoperative as taught by Kammiller."[68] The known technique of using a cutoff switch would have predictably resulted in protecting the inverter circuit. Therefore, it would have been within the skill of the ordinary artisan to use a cutoff switch in response to the actuation signal to protect the inverter.

E. "Obvious To Try"—Choosing From a Finite Number of Identified, Predictable Solutions, With a Reasonable Expectation of Success

To reject a claim based on this rationale, Office personnel must resolve the *Graham* factual inquiries. Office personnel must then articulate the following:

(1) a finding that at the time of the invention, there had been a recognized problem or need in the art, which may include a design need or market pressure to solve a problem;

(2) a finding that there had been a finite number of identified, predictable potential solutions to the recognized need or problem;

(3) a finding that one of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success; and

(4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

The rationale to support a conclusion that the claim would have been obvious is that "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103."[69] If any of these findings cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art.

Example 1: The claimed invention in *Pfizer, Inc.* v. *Apotex, Inc.*[70] was directed to the amlodipine besylate drug product, which is commercially sold in tablet form in the United States under the trademark Norvasc®. At the time of the invention, amlodipine was known as was the use of besylate anions. Amlodipine was known to have the same therapeutic properties as were being claimed for the amlodipine besylate but Pfizer discovered that the besylate form had better manufacturing properties (*e.g.*, reduced "stickiness").

Pfizer argued that the results of forming amlodipine besylate would have been unpredictable, and therefore were nonobvious. The court rejected the notion that unpredictability could be equated with nonobviousness here, because there were only a finite number (53) of pharmaceutically acceptable salts to be tested for improved properties.

The court found that one of ordinary skill in the art having problems with the machinability of amlodipine would have looked to forming a salt of the compound and would have been able to narrow the group of potential salt-formers to a group of 53 anions known to form pharmaceutically acceptable salts, which would be an acceptable number to form "a reasonable expectation of success."

Example 2: The claimed invention in *Alza Corp.* v. *Mylan Laboratories, Inc.*[71] was drawn to sustained-release formulations of the drug oxybutynin in which the drug is released at a specified rate over a 24-hour period. Oxybutynin was known to be highly water-soluble, and the specification had pointed out that development of sustained-release formulations of such drugs presented particular problems.

A prior art patent to Morella had taught sustained-release compositions of highly water-soluble drugs, as exemplified by a sustained-release formulation of morphine. Morella had also identified oxybutynin as belonging to the class of highly water-soluble drugs. The Baichwal prior art patent had taught a sustained-release formulation of oxybutynin that had a different release rate than the claimed invention. Finally, the Wong prior art patent had taught a generally applicable method for delivery of drugs over a 24-hour period. Although Wong mentioned applicability of the disclosed method to several categories of drugs to which oxybutynin belonged, Wong did not specifically mention its applicability to oxybutynin.

The court found that because the absorption properties of oxybutynin would have been reasonably predictable at the time of the invention, there would have been a reasonable expectation of successful development of a sustained-release formulation of oxybutynin as claimed. The prior art, as evidenced by the specification, had recognized the obstacles to be overcome in development of sustained-release formulations of highly water-soluble drugs, and had suggested a finite number of ways to overcome these obstacles. The claims were obvious because it would have been obvious to try the known methods for formulating sustained-release compositions, with a reasonable expectation of success. The court was not swayed by arguments of a lack of absolute predictability.

Example 3: The claimed invention in *Ex parte Kubin*[72] was an isolated nucleic acid molecule. The claim stated that the nucleic acid encoded a particular polypeptide. The encoded polypeptide was identified in the claim by its partially specified sequence, and by its ability to bind to a specified protein.

A prior art patent to Valiante taught the polypeptide encoded by the claimed nucleic acid, but did not disclose either the sequence of the polypeptide, or the claimed isolated nucleic acid molecule. However, Valiante did disclose that by employing conventional methods, such as those disclosed by a prior art laboratory manual by Sambrook, the sequence of the polypeptide could be determined, and the nucleic acid molecule could be isolated. In view of Valiante's disclosure of the polypeptide, and of routine prior art methods for sequencing the polypeptide and isolating the nucleic acid molecule, the Board found that a person of ordinary skill in the art would have had a reasonable expectation that a nucleic acid molecule within the claimed scope could have been successfully obtained.

Relying on *In re Deuel,* Appellant argued that it was improper for the Office to use the polypeptide of the Valiante patent together with the methods described in Sambrook to reject a claim drawn to a specific nucleic acid molecule without providing a reference showing or suggesting a structurally similar nucleic acid molecule. Citing *KSR,* the Board stated that "when there is motivation to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense." The Board noted that the problem facing those in the art was to isolate a specific nucleic acid, and there were a limited number of methods available to do so. The Board concluded that the skilled artisan would have had reason to try these methods with the reasonable expectation that at least one would be successful. Thus, isolating the

[67] 851 F.2d 1401, 7 USPQ2d 1500 (Fed. Cir. 1988).

[68] *Id.* at 1403, 7 USPQ2d at 1502.

[69] *KSR,* 550 U.S. at __, 82 USPQ2d at 1397.

[70] 480 F.3d 1348, 82 USPQ2d 1321 (Fed. Cir. 2007).

[71] 464 F.3d 1286, 80 USPQ2d 1001 (Fed. Cir. 2006).

[72] 83 USPQ2d 1410 (Bd. Pat. App. & Int. 2007).

specific nucleic acid molecule claimed was "the product not of innovation but of ordinary skill and common sense."

F. Known Work in One Field of Endeavor May Prompt Variations of it for Use in Either the Same Field or a Different One Based on Design Incentives or Other Market Forces if The Variations Would Have Been Predictable to One of Ordinary Skill in the Art

To reject a claim based on this rationale, Office personnel must resolve the *Graham* factual inquiries. Office personnel must then articulate the following:

(1) a finding that the scope and content of the prior art, whether in the same field of endeavor as that of the applicant's invention or a different field of endeavor, included a similar or analogous device (method, or product);

(2) a finding that there were design incentives or market forces which would have prompted adaptation of the known device (method, or product);

(3) a finding that the differences between the claimed invention and the prior art were encompassed in known variations or in a principle known in the prior art;

(4) a finding that one of ordinary skill in the art, in view of the identified design incentives or other market forces, could have implemented the claimed variation of the prior art, and the claimed variation would have been predictable to one of ordinary skill in the art; and

(5) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

The rationale to support a conclusion that the claimed invention would have been obvious is that design incentives or other market forces could have prompted one of ordinary skill in the art to vary the prior art in a predictable manner to result in the claimed invention. If any of these findings cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art.

Example 1: The fact pattern in *Dann* v. *Johnston*[73] is set forth above in Example 1 in subsection III.D.

The court found that the problem addressed by applicant—the need to give more detailed breakdown by a category of transactions—was closely analogous to the task of keeping track of the transaction files of individual business units.[74] Thus, an artisan in the data processing area would have recognized the similar class of problem and the known solutions of the prior art and it would have been well within the ordinary skill level to implement the system in the different environment. The court held that "[t]he gap between the prior art and respondent's system is simply not so great as to render the system nonobvious to one reasonably skilled in the art."[75]

Example 2: The claimed invention in *Leapfrog Enterprises, Inc.* v. *Fisher-Price, Inc.*[76] was directed to a learning device to help young children read phonetically.

The claim read as follows:

An interactive learning device, comprising:

a housing including a plurality of switches;
a sound production device in communication with the switches and including a processor and a memory;
at least one depiction of a sequence of letters, each letter being associable with a switch; and
a reader configured to communicate the identity of the depiction to the processor,
wherein selection of a depicted letter activates an associated switch to communicate with the processor, causing the sound production device to generate a signal corresponding to a sound associated with the selected letter, the sound being determined by a position of the letter in the sequence of letter.

The court concluded that the claimed invention would have been obvious in view of the combination of two pieces of prior art, (1) Bevan (which showed an electro-mechanical toy for phonetic learning), (2) the Super Speak & Read device (SSR) (an electronic reading toy), and the knowledge of one of ordinary skill in the art.

The court made clear that there was no technological advance beyond the skill shown in the SSR device. The court stated that "one of ordinary skill in the art of children's learning toys would have found it obvious to combine the Bevan device with the SSR to update it using modern electronic components in order to gain the commonly understood benefits of such adaptation, such as decreased size, increased reliability, simplified operation, and reduced cost. While the SSR only permits generation of a sound corresponding to the first letter of a word, it does so using electronic means. The combination is thus the adaptation of an old idea or invention (Bevan) using newer technology that is commonly available and understood in the art (the SSR)."

The court found that the claimed invention was but a variation on already known children's toys. This variation presented no nonobvious advance over other toys. The court made clear that there was no technological advance beyond the skill shown in the SSR device. The court found that "[a]ccomodating a prior art mechanical device that accomplishes that goal to modern electronics would have been reasonably obvious to one of ordinary skill in designing children's learning devices. Applying modern electronics to older mechanical devices has been commonplace in recent years."

Example 3: The claimed invention in *KSR International Co.* v. *Teleflex Inc.*[77] was an adjustable pedal assembly with a fixed pivot point and an electronic pedal-position sensor attached to the assembly support. The fixed pivot point meant that the pivot was not changed as the pedal was adjusted. The placement of the sensor on the assembly support kept the sensor fixed while the pedal was adjusted.

Conventional gas pedals operated by a mechanical link which adjusted the throttle based on the travel of the pedal from a set position. The throttle controlled the combustion process and the available power generated by the engine. Newer cars used computer controlled throttles in which a sensor detected the motion of the pedal and sent signals to the engine to adjust the throttle accordingly. At the time of the invention, the marketplace provided a strong incentive to convert mechanical pedals to electronic pedals, and the prior art taught a number of methods for doing so. The prior art (Asano) taught an adjustable pedal with a fixed pivot point with mechanical throttle control. The prior art ('936 patent to Byler) taught an electronic pedal sensor which was placed on a pivot point in the pedal assembly and that it was preferable to detect the pedal's position in the pedal mechanism rather than in the engine. The prior art (Smith) taught that to prevent the wires connecting the sensor to the computer from chafing and wearing out, the sensor should be put on a fixed part of the pedal assembly rather than in or on the pedal's footpad. The prior art (Rixon) taught an adjustable pedal assembly (sensor in the footpad) with an electronic sensor for throttle control. There was no prior art electronic throttle control that was combined with a pedal assembly which kept the pivot point fixed when adjusting the pedal.

The Court stated that "[t]he proper question to have asked was whether a pedal designer of ordinary skill, facing the wide range of needs created by developments in the field of endeavor, would have seen a benefit to upgrading

[73] 425 U.S. 219, 189 USPQ 257 (1976).

[74] *Id.* at 229, 189 USPQ at 261.

[75] *Id.* at 230, 189 USPQ at 261.

[76] 485 F.3d 1157, 82 USPQ2d 1687 (Fed. Cir. 2007).

[77] 550 U.S.__, 82 USPQ2d 1385 (2007).

Asano with a sensor." [78] The Court found that technological developments in the automotive design would have prompted a designer to upgrade Asano with an electronic sensor. The next question was where to attach the sensor. Based on the prior art, a designer would have known to place the sensor on a nonmoving part of the pedal structure and the most obvious nonmoving point on the structure from which a sensor can easily detect the pedal's position was a pivot point. The Court concluded that it would have been obvious to upgrade Asano's fixed pivot point adjustable pedal by replacing the mechanical assembly for throttle control with an electronic throttle control and to mount the electronic sensor on the pedal support structure.

Example 4: The claimed invention in *Ex parte Catan* [79] was a consumer electronics device using bioauthentication to authorize sub-users of an authorized credit account to place orders over a communication network up to a pre-set maximum sub-credit limit.

The prior art (Nakano) disclosed a consumer electronics device like the claimed invention, except that security was provided by a password authentication device rather than a bioauthentication device. The prior art (Harada) disclosed that the use of a bioauthentication device (fingerprint sensor) on a consumer electronics device (remote control) to provide bioauthentication information (fingerprint) was known in the prior art at the time of the invention. The prior art (Dethloff) also disclosed that it was known in the art at the time of the invention to substitute bioauthentication for PIN authentication to enable a user to access credit via a consumer electronics device.

The Board found that the prior art "shows that one of ordinary skill in the consumer electronic device art at the time of the invention would have been familiar with using bioauthentication information interchangeably with or in lieu of PINs to authenticate users." The Board concluded that one of ordinary skill in the art of consumer electronic devices would have found it obvious to update the prior art password device with the modern bioauthentication component and thereby gain, predictably, the commonly understood benefits of such adaptation, that is, a secure and reliable authentication procedure.

G. Some Teaching, Suggestion, or Motivation in the Prior Art That Would Have Led One of Ordinary Skill To Modify the Prior Art Reference or To Combine Prior Art Reference Teachings To Arrive at the Claimed Invention

To reject a claim based on this rationale, Office personnel must resolve the *Graham* factual inquiries. Office personnel must then articulate the following:

(1) a finding that there was some teaching, suggestion, or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings;

(2) a finding that there was reasonable expectation of success; and

(3) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

The rationale to support a conclusion that the claim would have been obvious is that "a person of ordinary skill in the art would have been motivated to combine the prior art to achieve the claimed invention and that there would have been a reasonable expectation of success." [80] If any of these findings cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art.

The courts have made clear that the teaching, suggestion, or motivation test is flexible and an explicit suggestion to combine the prior art is not necessary. The motivation to combine may be implicit and may be found in the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved.[81] "[A]n implicit motivation to combine exists not only when a suggestion may be gleaned from the prior art as a whole, but when the 'improvement' is technology-independent and the combination of references results in a product or process that is more desirable, for example because it is stronger, cheaper, cleaner, faster, lighter, smaller, more durable, or more efficient. Because the desire to enhance commercial opportunities by improving a product or process is universal—and even common-sensical—we have held that there exists in these situations a motivation to combine prior art references even absent any hint of suggestion in the references themselves. In such situations, the proper question is whether the ordinary artisan possesses knowledge and skills rendering him capable of combining the prior art references." [82]

IV. Applicant's Reply

Once Office personnel have established the *Graham* factual findings and concluded that the claimed invention would have been obvious, the burden then shifts to the applicant to (1) show that the Office erred in these findings, or (2) provide other evidence to show that the claimed subject matter would have been nonobvious. 37 CFR 1.111(b) requires applicant to distinctly and specifically point out the supposed errors in the Office's action and reply to every ground of objection and rejection in the Office action. The reply must present arguments pointing out the specific distinction believed to render the claims patentable over any applied references.

If an applicant disagrees with any factual findings by the Office, an effective traverse of a rejection based wholly or partially on such findings must include a reasoned statement explaining why the applicant believes the Office has erred substantively as to the factual findings. A mere statement or argument that the Office has not established a *prima facie* case of obviousness or that the Office's reliance on common knowledge is unsupported by documentary evidence will not be considered substantively adequate to rebut the rejection or an effective traverse of the rejection under 37 CFR 1.111(b). Office personnel addressing this situation may repeat the rejection made in the prior Office action and make the next Office action final. *See* MPEP § 706.07(a).

V. Consideration of Applicant's Rebuttal Evidence

Office personnel should consider all rebuttal evidence that is timely presented by the applicants when reevaluating any obviousness determination. Rebuttal evidence may include evidence of "secondary considerations," such as "commercial success, long felt but unsolved needs, [and] failure of others"[83], and may also include evidence of unexpected results. As set forth in section III. above, Office personnel must articulate findings of fact that support the rationale relied upon in an obviousness rejection. As a result, applicants are likely to submit evidence to rebut the fact finding made by Office personnel. For example, in the case of a claim to a combination, applicants may submit evidence or argument to demonstrate that:

(1) one of ordinary skill in the art could not have combined the claimed elements by known methods (e.g., due to technological difficulties);

(2) the elements in combination do not merely perform the function that each element performs separately; or

(3) the results of the claimed combination were unexpected.

[78] *Id.* at__, 82 USPQ2d at 1399.

[79] 83 USPQ2d 1569)Bd. Pat. App. & Int.

[80] *DyStar Textilfarben GmbH & Co. Deutschland KG* v. *C.H. Patrick Co.*, 464 F.3d 1356, 1360, 80 USPQ2d 1641, 1645 (Fed. Cir. 2006).

[81] *Id.* at 1366, 80 USPQ2d at 1649.

[82] *Id.* at 1368, 80 USPQ2d at 1651.

[83] *Graham* v. *John Deere Co.*, 383 U.S. at 17, 148 USPQ at 467.

Once the applicant has presented rebuttal evidence, Office personnel should reconsider any initial obviousness determination in view of the entire record.[84] All the rejections of record and proposed rejections and their bases should be reviewed to confirm their continued viability. The Office action should clearly communicate the Office's findings and conclusions, articulating how the conclusions are supported by the findings. The procedures set forth in MPEP § 706.07(a) are to be followed in determining whether an action may be made final.

See MPEP § 2145 concerning consideration of applicant's rebuttal evidence. See also MPEP § 716 to § 716.10 regarding affidavits or declarations filed under 37 CFR 1.132 for purposes of traversing grounds of rejection.

[84] *See, e.g., In re Piasecki,* 745 F.2d 1468, 1472, 223 USPQ 785, 788 (Fed. Cir. 1984); *In re Eli Lilly & Co.,* 90 F.2d 943, 945, 14 USPQ2d 1741, 1743 (Fed. Cir. 1990).

Dated: October 3, 2007.

Jon W. Dudas,

Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office.

[FR Doc. E7–19973 Filed 10–9–07; 8:45 am]

BILLING CODE 3510–16–P

DEPARTMENT OF DEFENSE

Office of the Secretary

[Transmittal Nos. 08–09]

36(b)(1) Arms Sales Notification

AGENCY: Department of Defense, Defense Security Cooperation Agency.

ACTION: Notice.

SUMMARY: The Department of Defense is publishing the unclassified text of a section 36(b)(1) arms sales notification. This is published to fulfill the requirements of section 155 of Public Law 104–164 dated 21 July 1996.

FOR FURTHER INFORMATION CONTACT: Ms. B. English, DSCA/DBO/CFM, (703) 601–3740.

The following is a copy of a letter to the Speaker of the House of Representatives, Transmittals 08–09 with attached transmittal, policy justification, and Sensitivity of Technology.

Dated: October 3, 2007.

L.M. Bynum,

OSD Federal Register Liaison Officer, Department of Defense.

BILLING CODE 5001–06–M

EXHIBIT 42 - 47
REDACTED